



DRUG UTILISATION STUDY OF ANTI-EPILEPTIC DRUGS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Introduction: Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process. 70 million people have epilepsy worldwide and nearly 90% of them are found in developing regions. Many patients have to be on treatment for a long period. Studies on antiepileptic drug utilization are important for the optimization of drug therapy and drug control. **Aim:** To study drug utilization pattern of antiepileptic drugs. **Methods:** This observational, cross-sectional study was conducted in Pune, India. Cases taking antiepileptic drugs for Epilepsy and seeking care in Dr. D.Y. Patil Hospital OPD and fulfilling the criteria were considered. Prescription of at least one Antiepileptic drug (AED) was the most important criteria. Evaluation was done on the basis of prescription data recorded. **Results and Discussion:** Out of total 150 cases, in 48 cases (32%) single conventional AEDs was prescribed & in 10 cases (6.6%) single newer AEDs were prescribed. In 92 cases (61.3%) two or more AEDs were prescribed. Among total 293 prescribed AEDs, 214 prescription (73%) were conventional AEDs and 79 prescription (27%) were newer AEDs. The most commonly prescribed drug was Valproate (28.6%), followed by carbamazepine (23.8%) and phenytoin (18%). Among the newer AEDs prescription the commonest was levetiracetam (16.7%) followed by lamotrigine (7.8%). In GTCS the most common prescription was carbamazepine (45.3%) and Valproate (45.3%). **Conclusion:** Based on the findings of our study we conclude that polytherapy was commonly used in all types of epileptic seizures & the most commonly prescribed AED was sodium valproate, followed by carbamazepine, phenytoin and the new generation AED, Levetiracetam.

KEYWORDS: Epilepsy, Drug Utilisation study, Prescription pattern, Monotherapy, Polytherapy, Antiepileptics, Phenytoin.

INTRODUCTION

Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process.^[1] It is the second most common and frequently encountered neurological condition that imposes heavy burden on individuals, families, and also on healthcare systems. As per a recent study, 70 million people have epilepsy worldwide and nearly 90% of them are found in developing regions.

The backbone of treatment of epilepsy is pharmacological therapy with antiepileptic drugs (AEDs). Treatment options for epilepsy include the older AEDs (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, and valproic acid) as well as several newer drugs (Levetiracetam, felbamate,

gabapentin, lacosamide, lamotrigine, oxcarbazepine, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide).^[2]

In the past decade many advances has been brought to the treatment of epilepsy, including many new pharmacological agents. Several new AEDs like gabapentin, lamotrigine, felbamate, topiramate, oxcarbazepine, etc have been approved for epilepsy therapy with the aim of broadening treatment options, improve seizure control and tolerability. Some of them can be used as monotherapy, without development of tolerance. They have high response rate, good seizure control and tolerability, when used as adjuvant therapy. These properties make them useful even in patients with refractory epilepsy. In addition to the above properties,

they are also safer in women and have less drug interactions.

Once on treatment, many patients have to be on treatment for a long period. Studies on antiepileptic drug utilization are important for the optimization of drug therapy and drug control. With this background, the present research was aimed to study drug utilization pattern of antiepileptic drugs in the treatment of epilepsy.

Aim

Aim of this research was to study drug utilization pattern of antiepileptic drugs.

Objectives

This study was conducted with the following objectives:

- To study and compare monotherapy and combined anti epileptic drug therapy.
- To study and compare conventional and newer anti epileptic drug therapy.

METHODS

The study was approved by Institutional Ethics Committee before the beginning of the study. The observational cross-sectional study was conducted in Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune, Maharashtra conducted from Jan 2016 to April 2017.

Taking prescription rate of 31.3% (Haroon A et al^[3]) monotherapy of antiepileptic drugs for epilepsy cases, absolute precision of 5% (α error) and design effect of 1, the calculated sample size was 142 with 80% power of the study (β error) by using OperEpi software⁴. This was rounded to nearest higher number, 150. So the final sample size was kept 150.

Eligibility Criteria

Inclusion Criteria

Cases with following criteria were included in the study:

- Patients between 18 years and 70 years who were on antiepileptic medications
- Patients of either gender
- Diagnosed cases of epilepsy who were willing to participate in the study
- Cases of status epilepticus

Exclusion Criteria

Cases with following criteria were excluded from the study.

- Patients below 18 and above 70 years of age.
- Patients with lack of proper prescription records.
- Patients who are on other concomitant medication for some other chronic diseases.

All cases taking antiepileptic drugs for Epilepsy and seeking care in Dr. D.Y. Patil Hospital out patient department and were full filling the above mentioned criteria were considered for inclusion in the study.

Prescription of at least one Antiepileptic drug (AED) was the most important criteria.

Cases giving consent were recruited consecutively till the desired sample size was achieved.

Following evaluation tools were used for data collection:

- Medical case record sheets, specifically prescriptions of the patients were reviewed.
- Type of drug, number of drug, dose and other details were extracted from the prescription.

Statistical Analysis

Quantitative variables are presented as percentage. Appropriate statistical calculations are done for analysis. During analysis monotherapy of AEDs was compared with poly-therapy and conventional AEDs prescriptions were compared with newer AEDs.

RESULTS

The present research was conducted among 150 patients who were prescribed antiepileptic drugs. 102 cases(68%) of the cases were males whereas, 48 cases (32%) were females. The maximum number of cases were in the age group of 21-30 years (40%) followed by 31-40years (21.3%), 18-20years(19.3%), 41-50 years (10%), and 51-60 years (6.7%).

Figure 1 show distribution of study cases according to type of seizure. Out of total 150 cases, more than half of the cases (n=86, 57.3%) were having Generalised Tonic Clonic Seizures, followed by Complex Partial Seizures (n=18, 12%) and tonic seizure ((n=18, 12%). Other type includes Simple Partial Seizures (5.3%), Myoclonic Seizures (8%), and Absence Seizures (5.3%).

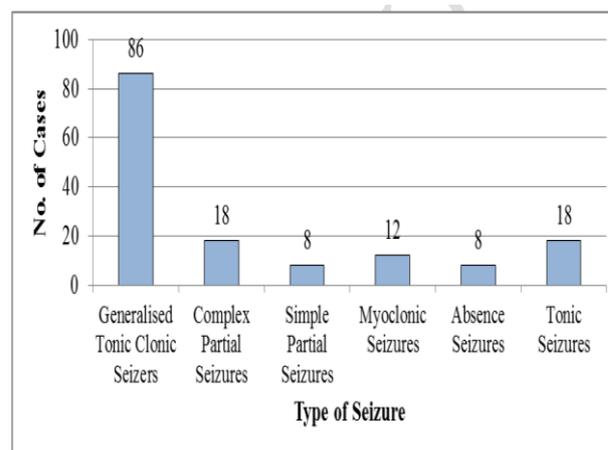


Figure. 1: Distribution of cases according to the type of epilepsy.

Figure 2 show distribution of study cases according to number of AEDs Prescribed. Out of total 150 cases, in 58 cases (38.6%) single AEDs was prescribed. In 46 cases (30.7%) two AEDs were prescribed. In 41 cases (27.3%) three AEDs were prescribed. In 5 cases (3.3%) four AEDs were prescribed.

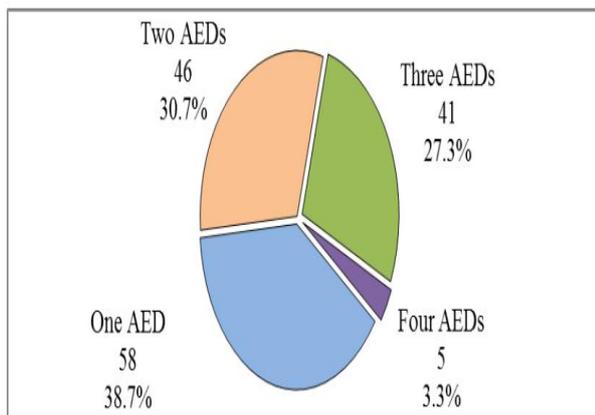


Figure. 2: Distribution of cases according to number of AEDs Prescribed.

Figure 3 show distribution of study cases according to type of AEDs therapy. Among total 293 prescribed AEDs, 214 prescription (73%) were conventional AEDs and 79 prescription (27%) were newer AEDs.

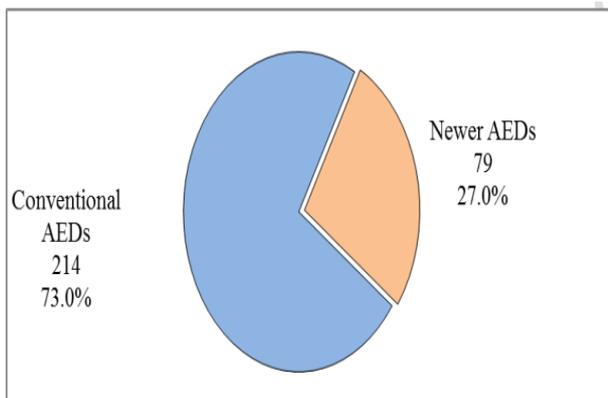


Figure. 3: Distribution of cases according to type of therapy.

Figure 4 show distribution of study cases according to type of AED therapy prescribed. Out of total 150 cases, in 48 cases (32%) single conventional AEDs was prescribed. In 10 cases (6.6%) single newer AEDs were prescribed. In 92 cases (61.3%) two or more AEDs were prescribed.

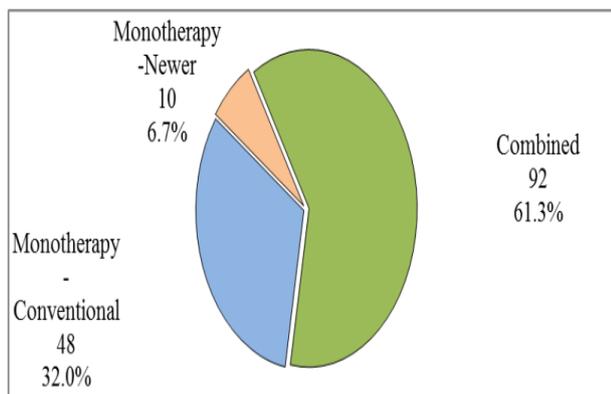


Figure. 4: Distribution of cases according to number of AEDs Prescribed.

Figure 6 show drug reactions reported by the cases after taking AEDs. Among total 150 cases, in 7 cases (4.7%) developed drowsiness. 3 cases (2.0%) experienced Drowsiness with subtle imbalance, 2 cases had gum swelling and one case had Decreased memory and learning. So, total 13 cases (8.7%) had adverse drug reactions.

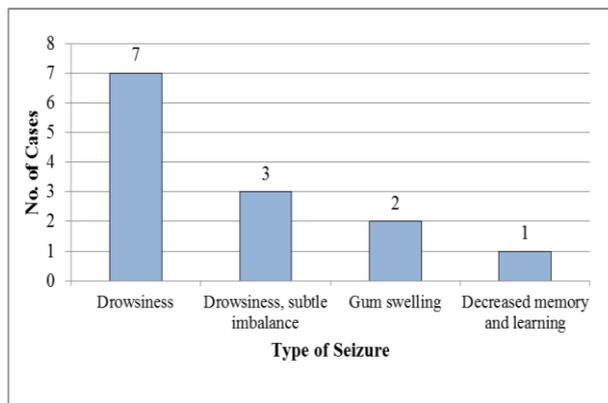


Figure. 6: Adverse drug reactions reported among the study cases.

Table 1 shows prescriptions of individual AED in various types of seizures. In GTCS, the most common prescription was carbamazepine (45.3%) and Valproate (45.3%). In CPS, the most common prescription was carbamazepine (45.3%) followed by Valproate (83.3%). In SPS, the most common prescription was valproate (75%) followed by carbamazepine (44.2%). In MS, the most common prescription was valproate (66.7%) followed by Levetiracetam (50%). In AS, the most common prescription was carbamazepine (62.5%) and Levetiracetam (62.52%). In TS, the most common prescription was Levetiracetam (38.9%) followed by Valproate (27.8%).

Table. 1: Distribution of prescribed AEDs according to type of seizures.

AEDs	Type of Seizures					
	GTCS	CPS	SPS	MS	AS	TS
Conventional						
Phenobarbital	3 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Phenytoin	36 (41.9)	10 (55.6)	4 (50)	0 (0)	0 (0)	1 (5.6)
Carbamazepine	39 (45.3)	16 (88.9)	5 (62.5)	0 (0)	0 (0)	4 (22.2)
Valproate	39 (45.3)	15 (83.3)	6 (75)	8 (66.7)	5 (62.5)	5 (27.8)
Clonazepam	2 (2.3)	2 (11.1)	0 (0)	0 (0)	0 (0)	0 (0)
Newer						
Levetiracetam	22 (25.6)	7 (38.9)	2 (25)	6 (50)	5 (62.5)	7 (38.9)
Oxcarbazepine	2 (2.3)	1 (5.6)	0 (0)	1 (8.3)	0 (0)	0 (0)
Zonisamide	2 (2.3)	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)
Lamotrigine	10 (11.6)	3 (16.7)	2 (25)	2 (16.7)	2 (25)	4 (22.2)
Total Cases	86	18	8	12	8	18

GTCS= Generalised Tonic Clonic Seizers; CPS= Complex Partial Seizures

SPS=Simple Partial Seizures; MS=Myoclonic Seizures; AS= Absence Seizures

TS= Tonic Seizures

DISCUSSION

Epilepsy is a chronic disorder characterized by recurrent and unprovoked seizures and is one of the most common neurological disorders in the adult. Different anti-epileptic drugs (AEDs) are used for the symptomatic treatment of different forms of epileptic seizures. Treatment should aim at controlling symptoms associated with the lowest possible incidence of adverse drug reactions (ADRs) allowing the individual to become an active member of the community.

In our study, out of total 150 cases, 102 (68%) were male and 48 (32%) were female. The male to female ratio was 2.125:1. Many studies found similar results. A study by Hauser WA *et al*^[5], Gnanamuthu C *et al*^[6], Chen LC *et al*^[7], and RadhakrishnanKet *al*^[8] found higher male indicating seizures are more common in male. However, the gender distribution of a study by Hanssens Y *et al*^[9] contradicts the previous findings that epileptic seizures are more common in men than in women. In this study higher proportion of women were reported.

More than half of the cases (n=86, 57.3%) were having Generalised Tonic Clonic Seizures, followed by Complex Partial Seizures (n=18, 12%) and tonic seizures (n=18, 12%). Other types included Simple Partial Seizures (5.3%), Myoclonic Seizures (8%), and Absence Seizures (5.3%). In agreement with Gnanamuthu's preliminary findings, generalized seizures followed by partial seizures were the most common type of epileptic seizures encountered in this study as well as a study done in Oman.^[10]

In our study conventional drugs were prescribed more commonly compared to newer AEDs. There were total 293 AED prescriptions among 150 cases. Out of total 293 AEDs prescriptions, the most commonly prescribed drug was Valproate (28.6%), followed by carbamazepine (23.8%) and phenytoin (18%). Among the newer AEDs prescription the commonest was levetiracetam (16.7%) followed by lamotrigine (7.8%). In our study, in GTCS the most common prescription was carbamazepine (45.3%) and Valproate (45.3%). In CPS the most common prescription was carbamazepine (45.3%) followed by Valproate (83.3%). In SPS the most common prescription was valproate (75%) followed by carbamazepine (62.5%). In MS the most common prescription was valproate (66.7%) followed by Levetiracetam (50%). In AS the most common prescription was carbamazepine (62.5%) and Levetiracetam (62.52%). In TS the most common prescription was Levetiracetam (38.9%) followed by Valproate (27.8%).

A comparison with the AED utilization pattern in other countries is given in Table 2. Although these studies differ in design and some of them date from the early 1990s, AEDs such as phenytoin and phenobarbital still belong to the anti-epileptic armamentarium and are even considered first-line anti-epileptic agents for certain forms of epileptic seizures. They still account for well over 20% of prescriptions.^[11,12,13,14]

Table. 2: Comparison of anti-epileptic drug pattern with other countries.

Country	Total percentage for each AED			
	Valproate	Carbamazepine	Phenytoin	Phenobarbital
USA ⁸³	13	31	48	18
UK ⁸⁵	25	30	30	18
The Netherlands ⁸⁴	25	49	24	12
France ⁸⁶	59	33	–	10
India ⁷⁶	21	44	25	8
Bulgaria ⁸⁷	23	39	6	12
Taiwan ⁷⁵	31	57	32	14
Present study	27.9	23.8	18	1

In our study, among total 293 prescribed AEDs, 214 prescriptions (73%) were conventional AEDs and 79 prescriptions (27%) were newer AEDs. 48 cases (32%) single conventional AEDs were prescribed. In 10 cases (6.6%) single newer AEDs were prescribed. In 92 cases (61.3%) two or more AEDs were prescribed. 58 were monoprescription while remaining 92 prescriptions there were multiple AEDs. In these total 235 AEDs were there. Among them Out of total 235 prescribed AEDs, 58 (24.6%) conventional AEDs were combined with other conventional AEDs. In remaining 177 prescribed AEDs, 108 conventional AEDs were combined with 69 newer AEDs.

Overall, most frequently prescribed AEDs were phenytoin followed by valproate, oxcarbazepine, and carbamazepine/clonazepam. Overall pregabalin was the most common AED prescribed, followed by phenytoin in a study by Patel PM *et al.*^[15] Hsieh *et al.* study conducted in Taiwan revealed that carbamazepine and valproic acid were the most common AEDs used and among the newer generation of AEDs, gabapentin was the most frequently used.^[16] These findings differ with our finding; the reason may be the higher prevalence of non-epileptic conditions in our study than another study. Mathur *et al.* study in Hyderabad showed similar finding.^[17] Different finding seen in Arulkumaran *et al.* in Coimbatore, India as valproic acid was commonest AED prescribed followed by carbamazepine, phenytoin, and oxcarbazepine.^[18]

The dissimilarity is seen in utilization pattern of various AEDs in both Indian studies and also in studies conducted out of India. This may be because of the prevalence of different types of epilepsy. Pregabalin was most common AED prescribed for both conditions. Oxcarbazepine was the second most commonly prescribed AED for neuropathy, clonazepam for psychomotor disorders. Arulkumaran *et al.* study in Coimbatore showed that oxcarbazepine followed by gabapentin were commonly prescribed AEDs for non-epileptic condition.^[18]

In our study, among total 150 cases, 7 cases (4.7%) developed drowsiness, 3 cases (2.0%) experienced drowsiness with subtle imbalance, 2 cases had gum swelling and one case had decreased memory and

learning. So, total 13 cases (8.7%) had adverse drug reactions. So the overall rate was low. A study by MathurS *et al.*^[17] reported even lower overall incidence of adverse drug reactions (ADRs) (13 patients out of 278 i.e. 4.67%). In this study Phenytoin and Carbamazepine contributed equally to the occurrence of ADRs (six patients each). Drowsiness, imbalance, gum swelling, decreased memory and learning were the ADRs reported by patients on Phenytoin in our study. Most of these correspond well with the known adverse effect profile of Phenytoin.^[19]

In our study, among total 214 conventional drug prescriptions, 55.6% were for Generalised Tonic Clonic Seizures, 24.8% were for Complex Partial Seizures, 8.9% were for Simple Partial Seizures, 3.7% were for Myoclonic Seizures, 2.3% were for Absence Seizures, and 4.7% were for Tonic Seizures. Among total 79 newer AED prescriptions, 45.6% were for Generalised Tonic Clonic Seizures, 13.9% were for Complex Partial Seizures, 6.3% were for Simple Partial Seizures, 11.4% were for Myoclonic Seizures, 8.9% were for Absence Seizures, and 13.9% were for Tonic Seizures.

CONCLUSION

Based on the findings of our study and discussion we would like to conclude that

- Generalized seizures were most prominent, probably explaining the unique drugutilization profile.
- Most of the seizures were idiopathic in origin.
- Polytherapy was commonly used in all types of epileptic seizures.
- The selection of the AEDs corresponds well with the known efficacy profile for specific epileptic seizure types.
- The most commonly prescribed AED was sodium valproate, followed by carbamazepine, phenytoin and the new generation AED, Levetiracetam.
- Selection of AEDs was commonly not related to age and gender of the case.
- The overall incidence of adverse drug reactions was low, similar to other studies.

Declarations

Funding: No funding sources.

Conflict of Interest: Nil.

Ethical Approval: The study was approved by **Institutional Ethics Committee (IEC)**

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