



DRUG UTILIZATION PATTERN OF ANTIEPILEPTIC DRUGS: A PHARMACOEPIDEMIOLOGIC AND PHARMACOVIGILANCE STUDY IN A TERTIARY TEACHING HOSPITAL IN INDIA

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ABSTRACT

Objective: Epilepsy is the second most common chronic neurological condition seen by neurologists. It is estimated that there are 55, 00,000 persons with epilepsy in India. So, the present study aims at getting an insight into the type of epileptic seizures prevalent in a tertiary referral teaching Hospital in eastern India, to describe the drug utilization pattern of antiepileptic drugs (AEDs) for the management of various forms of epileptic seizures over a period of one year and to investigate the pattern and extent of adverse drug reactions (ADRs) with AEDs.

Methods: Data from five hundred twenty eight patients with epilepsy at the outpatient of Neurology Department, SCB Medical College and Hospital, Cuttack was collected according to detailed semi-structured questionnaire. The data includes demographic data, AEDs data and ADR data.

Results and Discussion: Tonic clonic seizures were most prominent followed by complex partial seizures. Most of patients are young and epileptic seizures are more common in man. 47% of cases are refractory. Polytherapy was most frequently used in all type of epileptic seizures. Sodium Valproate was the most frequently prescribed AED followed by Phenyton sodium and Carbamazepine. The drugs prescribed are mainly from the Essential drug list. The ADRs are found to mild and predominant in female.

Conclusion: This study strongly highlights the need for therapeutic drug monitoring of epileptic patients. Measures should be taken to improve rational use of antiepileptic drugs to minimise the number of refractory cases of epilepsy. There is under utilization of newer AEDs. Inclusion of newer AEDs like Lamotrigine, Topiramate etc in the Essential Drug List is recommended. Female patients need special attention during medication.

Key words: Antiepileptic drugs; Pharmacoepidemiology; Pharmacovigilance; Teaching hospital.

INTRODUCTION

Epilepsy is one of the most common neurological disorders characterized by recurrent and unprovoked seizures. The incidence and prevalence of epilepsy shows substantial geographical heterogeneity.¹ While the incidence of this disorder in most developed countries is between 50 to 100 cases per 100,000 population per year and prevalence is about 5-8 cases per 1000 population,² In developing countries the prevalence has been reported to be more than 40 per 1000 population.³ Also the distribution of epilepsy in the population is not uniform across age groups.⁴ Epilepsy is the second most common chronic neurological condition seen by neurologists. It is estimated that there are 55, 00,000 persons with epilepsy in India.⁵

Available antiepileptic drugs (AEDs) share three basic mechanisms of action. They either reduce repetitive firing due to interference with sodium currents, augment γ -amino butyric acid (GABA) neurotransmission or reduce transient Ca^{++} currents.⁶ Later to 1993 some new drugs have entered the worldwide market such as Felbamate, Gabapentin, Lamotrigine, Topiramate, Zonisamide, Levetiracetam, Vigabatrin etc.⁷ The growing number of newly approved drugs have contributed to the increased adverse drug reactions (ADRs).⁸

Adverse effects are highly prevalent in the drug treatment of epilepsy. Polytherapy is a common practice for the management of epilepsy despite of significant increase in side effects.⁹ Lack of systematic pharmacoepidemiologic studies investigating drug use pattern and ADRs related to AEDs has made it difficult to assess accurately the exact incidence of AED related ADRs.¹⁰

SCB Medical College, Cuttack is a tertiary care teaching hospital in eastern region of India with a potential of 750 beds and special facilities for epileptic patients. It provides health care for more than 500,000 people of eastern India. It was opened in 1943. In eastern India, the large majority of neurological patients are treated at tertiary referral centres. There is hardly any epidemiological data on epilepsy generated from eastern India. It is also one of the 24 peripheral centres under the National Pharmacovigilance Programme in India.

The present study aims at getting an insight into the type of epileptic seizures prevalent in this tertiary referral centre, to describe the drug utilization pattern of AEDs for the management of various forms of epileptic seizures over a period of one year and to investigate the pattern and extent of ADRs with AEDs.

METHODS

This study was carried out over one year period (from 1st March 2009 to 28th February 2010). All prescriptions issued during this period immediately following each day's consultation with the neurologist were copied out and recorded on case record forms. Our study was conducted on a patient pool of 528 people. Only people with epilepsy and treated with an AED are included in this study.

The following data were retrieved retrospectively from the prescription and the patient's medical records: demographic data (age and gender), known or newly diagnosed epileptic patient, type and aetiology of epileptic seizure, AED data (i.e. type of drug and formulation and availability), and selection of drugs from Essential Drug List (EDL) and ADR data. The type of reaction, causality, onset, severity and outcomes of ADRs were collected according to a detailed semi-structured questionnaire.¹¹

If an ADR was detected it was subjected to WHO probability scale to assess the causality relationship between the medication and the adverse reaction with the help of a neurologist.¹² Afterwards the severity of the reaction was determined mild, moderate or serious.¹³ When an ADR was associated with more than one medication, the agent most likely to be responsible for the adverse reaction was included in the final analysis.

The epileptic seizures were grouped according to the classification of the International League against Epilepsy¹⁴: Complex partial, Simple partial, Tonic-clonic, Absence, Myoclonic, Clonic, Tonic, Atonic and Status epilepticus. The following aetiologies were considered: idiopathic, trauma, infection, tumour, drug induced, systemic disease, metabolic/toxic and degenerative.

STATISTICAL ANALYSIS

Descriptive statistical analysis using SPSS was carried out. Frequencies, mean values and percentages were obtained.

Table -1: Demographic Characteristics of the study population being treated with AEDs (n=528)

Sex	No. of Patients(n)	Percentage
Male	312	59.09
Female	216	40.91

Age (years)	No. of Patients(n)	Percentage
1-14	252	47.72
15-20	116	21.96
21-30	92	17.42
31-40	40	7.57
41-50	16	3.03
51-65	8	1.51
≥65	4	0.75

Table -2: Types of epileptic seizure and aetiology in study population (n=528)

Classification	No. of Patients(n)	Percentage
Tonic-clonic seizure	261	49.43
Complex partial seizure	218	41.28
Myoclonic seizure	32	6.06
Tonic seizure	5	0.85
Atonic seizure	14	2.65
Absence seizure	4	0.75
Simple partial seizure	4	0.75

Aetiology	No. of Patients(n)	Percentage
Idiopathic	442	83.71
Infection	34	6.43
Systemic disease	20	3.78
Trauma	16	3.03
Metabolic/toxic	14	2.65
Degenerative	2	0.38

Table -3: Level of severity, type of ADR and sex wise distribution (n=86) in patients receiving AEDs

Level of severity	No. of reaction	Percentage
Mild	34	39.53
Moderate	28	32.55
Severe	24	27.90

Causality analysis	No. of reaction	Percentage
Probable	46	53.48
Possible	22	25.58
Definite	18	20.93
Unlikely	-	-

Sex	No. of reaction	Percentage
Male	38	44.18
Female	48	55.81

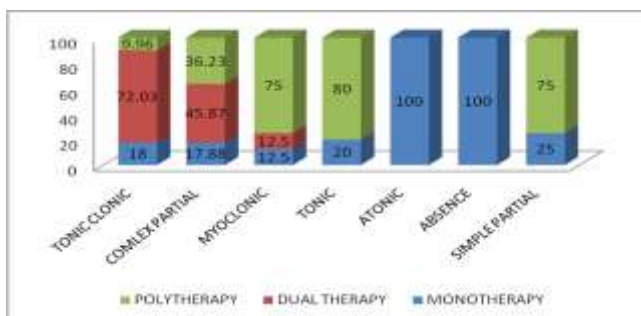


Figure -1: Percentage of mono/dual/polytherapy in different types of epileptic seizures (n=528)

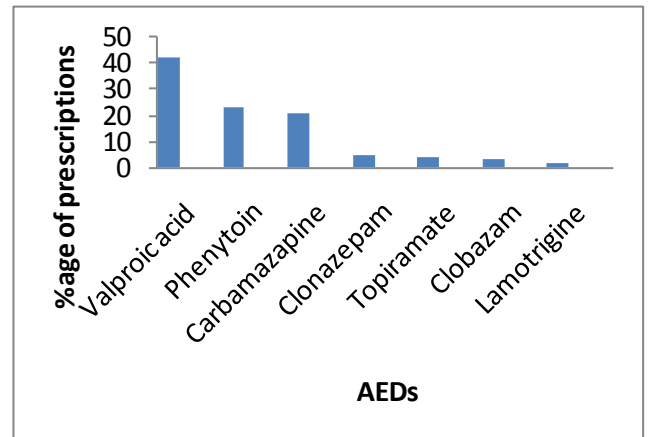


Figure -2: Distribution of the anti-epileptic drugs prescribed (n=528)

RESULTS

Prescriptions originating from 528 patients with a confirmed diagnosis of epileptic seizures and treated with AEDs were collected over one year period. The demographic characteristics of these patients are presented in Table 1. The age ranged from 1 to 72 years with 87% patients being younger than 30 years of age. Over 59% of patients encountered are males.

The type of epileptic seizures as well as the aetiology is presented in Table -2. Out of all patients 47.72% cases are found to be refractory. Generalised tonic-clonic seizures are the most prevalent of all types of epileptic seizures which accounted in 49.43% of patients. Idiopathic epilepsy was the most common cause of epileptic seizures (83.71%).

In this study population, 100 (18.93%) were prescribed an AED as monotherapy and 292 (55.30%) needed dual therapy (Figure 1). 136 (25.75%) patients were managed with Polytherapy (≥3 AEDs). Most of the polytherapy prescriptions consisted of triple therapy. Only one patient was administered with 4 AEDs.

Independent of the AED use profile (either monotherapy or combination therapy, Sodium Valproate (42.42%) was the most frequently prescribed AED followed by Phenytoin sodium (23.10%) and Carbamazepine (21.02%). The distribution of seizure type as a function of the AED in monotherapy is presented in Figure 2. The most frequently used combination therapy of AEDs consisted of Sodium Valproate/ Carbamazepine (28%) followed by Sodium Valproate/ Phenytoin (20%). 86.54% of the prescribed drugs are from the Essential drug list (EDL).

Among 528 patients with epilepsy 86 (16.28%) had ADR. Table-3 lists the level of severity, type of ADR and sex wise distribution in patients receiving AEDs. Most of the ADRs belonged to possible (52.48%) followed by probable (25.58%) categories. Highest percentage of patients showed mild ADR (39.53%). The ADRs are predominant in female (55.81%). The extent of ADRs with AED monotherapy was 12% and with polytherapy it was 17.28 %. Central Nervous system related ADRs (memory impairment, depression, dizziness, ataxia etc) were maximum in number (34.88%).

DISCUSSION

In our study almost 87% of patients were younger than 30 years of age. This contradicts the studies from western countries,^[15-17] where the onset of epileptic seizures is most frequent at the age extremes of life. However, the gender distribution of our study is similar to the previous findings that epileptic seizures are more common in men than in women.¹⁸⁻²⁰ Tonic Clonic seizures followed by complex partial seizure were most common type of epileptic seizure encountered in east India. Interestingly 47% of cases are refractory. This seizure profile appears to be unique and different from other studies in India.²⁰

The incidence of refractory epilepsy remains high despite the influx of many new AEDs over the past 10 years. Epidemiological data indicate that 20-40% of the patients with newly diagnosed epilepsy will become refractory to treatment²¹ So, a higher prevalence of refractory epilepsy in our study recommends a detailed approach to the management of chronic and refractory epilepsy. So there is a need for therapeutic drug monitoring of epileptic patients to know the cause of refractory epilepsy and measures should be taken to improve rational use of antiepileptic drugs to minimise the number of refractory cases of epilepsy.

Proper classification of the seizure type or epileptic syndrome is a key determinant in the choice of AED. In our study Valproic acid was the first line drug prescribed in tonic-clonic seizures. Carbamazepine was the AED of choice in complex partial seizures.

Our data indicated that polytherapy was the therapy of choice in majority of patient with partial or generalized seizure. This finding contradicts the finding in other studies.²²⁻²⁵ The reason for polytherapy may be attributed to higher incidence of refractory epilepsy in our study. Polytherapy increases the potential for drug-drug interaction, can increase the risk of chronic toxicity and is associated with a higher cost of medication. However, in polytherapy there is improved seizure control.

Valproic acid was the most frequently prescribed AED. In most of the prescriptions the physicians prefer classical AEDs. Newer drugs like Lamotrigine, Topiramate etc are not preferred which is unlike to other studies. The limited prescribing of newer AEDs indicated that these drugs are under used. Another cause may be that the drugs are selected from the EDL. Interestingly Phenobarbitone, which is one of the anti-epileptic armamentarium, was not prescribed in any of the prescriptions.²⁶

While effective pharmacological treatment of epilepsy is important, it is equally important to consider whether possible adverse events will outweigh benefits to patients. There are few outpatient ADR studies which may be due to the difficulties in identifying these ADRs and their associated risk factors. However, we have made an attempt for out-patient ADR study.²⁷

The demographic reports of various ADR epidemiological studies cited a predominance of the female over male. The observation in our study are similar to earlier studies.²⁸ The causality assessment revealed that most of the ADRs belong to possible followed by probable categories. This study contradicts the earlier findings.²⁹ Severity assessment showed highest percentage of mild reactions. Previous studies have shown larger percentage of ADR reports were from geriatric populations.³⁰ In present study most of the patients are young. This may be the reason for mild ADRs associated with AEDs.

Pharmacoresistant epilepsy or refractory epilepsy is associated with cognitive deficits and depressive disorder. This might be the reason of maximum number of central nervous system related ADRs in our study.³¹⁻³³

In recent times, there has been a concerted effort to ensure rational drug use. For standardization, the WHO and other official bodies have identified specific drug use indicators that include no. and cost of drugs, use of generic names of prescribed drugs and adherence to the essential drug list.³⁴ Our study reveals that doctors while prescribing AEDs adhere to the EDL.³⁵ However, some new drugs may be included in the EDL.

CONCLUSION

In our study tonic clonic seizures were most prominent followed by complex partial seizures. Most of patients are young and epileptic seizures are more common in man. Polytherapy was most frequently used in all type of epileptic seizures. The drugs prescribed are mainly from the Essential drug list. The ADRs are found to be mild and predominant in female.

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