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Research Article

A PROSPECTIVE AND OBSERVATIONAL STUDY OF USE OF ANTI-EPILEPTIC DRUGS IN A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

The prevalence and incidence of epilepsy is higher in developing countries than in developed countries. Understanding pattern and imperil factors of seizure cases will avail in suggesting congruous preventive measures. This study was carried out to assess the pattern of seizure, utilization pattern of anti-epileptic drugs, its management and compliance with the treatment. In a prospective study spanning six months (January to June 2016), the prescription data of 104 epileptic patients was collected from neurology Out Patient department (OPD) and the General Medicine Department of Osmania General Hospital, Hyderabad. Proximately half (55.76%) of the 104 cases belonged to productive age group (15-45 years) and 2/3rd (66.34%) were males. Majority (>60% cases) were unskilled workers and of low socio-economic status groups. Family history of seizures was present in 18.26% cases. Proportion of Generalized Tonic Clonic Seizure cases was 76.92%. Secondary seizures were seen in 28 (26.92%) cases with the most common cause being alcohol withdrawal (17.30%). Monotherapy was the most commonly followed treatment regimen and phenytoin was the most popular anti-epileptic drug (AED) utilised. Non-compliance with AEDs was seen in 27.88% cases. The overall incidence of adverse drug reactions was not very high. Phenytoin accounted for almost all of the ADRs collected and evaluated. Idiopathic generalized epilepsy was the commonest type of epilepsy recorded. Monotherapy was preferred in most cases and frequent use of newer AED namely levetiracetam. Seizure manifestations and treatment compliance vary widely in the studied population. In depth analysis of each seizure type will give more information about the factors associated with it.

Keywords: Compliance, Utilization Pattern, Risk Factors, Seizures, Treatment.

INTRODUCTION

Epilepsy is a mundane neurological disorder which demands immediate medical attention and often long term therapy. The incidence is approximately 0.3 – 0.5% in different world populations with a prevalence rate of five to ten per thousand people. Around 50 million people world-wide have epilepsy. [1]The prevalence and incidence of epilepsy is higher in developing countries than in developed countries. However, in developing countries, given the high incidence of epilepsy, the prevalence is relatively low, which may be due to the poor prognosis and high mortality for people with epilepsy. [2, 3] This poor prognosis is mainly because of a sizably voluminous treatment gap along with poor health seeking deportment of people[2]

The overall aim in treating epilepsy should be consummate control of seizures, without causing any untoward reaction due to the medication. A sizably voluminous number of drugs are currently available for the treatment of epilepsy. Older/conventional drugs like phenytoin, carbamazepine, valproic acid and ethosuximide are commonly utilized as first line drugs. They are relatively less sumptuous than the more incipient antiepileptics. Drugs like gabapentin, lamotrigine, vigabatrin, topiramate, tiagabine and zonisamide are the more incipient ones and currently utilized as integrate-on or alternative therapy. They have lesser deleterious effects and have few, if any, drug interactions[1, 2]. Some side effects may be mundane with the above mentioned drugs and include sedation and ataxia. They can be diverse as well, ranging from idiosyncratic reactions like bone marrow dejection (carbamazepine) to acute myopia and glaucoma (topiramate). Monotherapy is the conventional dictum, but polytherapy is needed for patients with multiple seizure types or refractory

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disease [3, 4, 5]. The current study endeavors to analyze the pattern of drug utilization in variants of epilepsy. The extent of polytherapy is withal looked into. The adverse drug reactions reported by the patients and their impact on the continuation of antiepileptic therapy are evaluated.

It is obligatory to understand the pattern of seizures at a tertiary care level, so that the congruous interventional measures according to the type of seizures and other issues may be addressed. Very few studies have been conducted in India in this regard. Besides, there is a desideratum for invigorating accommodations towards treatment and follow-up of this vulnerably susceptible group due to socio-economic factors and other factors.[5]With this background, the present study was conducted to assess the pattern of seizure cases at Osmania General Hospital, a tertiary care hospital in Hyderabad city.

About 50% of the patients become seizure free with the first drug endeavored and can lead a mundane life[6]. Seizure can be controlled with monotherapy in majority of them [7]. This conventionally requires meticulous and rigid adherence to drug regimens, which involve taking tablets conventionally, two or three times each day for many years, sometimes for a lifetime. Medicos often judge the efficacy of treatment by gross clinical replication. There are wide variations in each person's replication to treatment, and the plasma concentration of AEDs provides little information about a person's likelihood of reduction of seizures or side-effects. The available data on efficacy of drugs are mostly from the western studies [8]. But the drug replication and efficacy may vary depending on the genetic, environmental, pharmacodynamic and pharmacokinetic interaction in different racial groups. Moreover, the cost of AEDs often poses a treatment gap in management of epilepsy.

The present study was carried out to assess the pattern of seizure, its management and compliance with treatment. The objective is to identify the utilization pattern of anti-epileptic drugs (AEDs) in different types of epilepsy and the extent of polypharmacy, and also to evaluate the adverse drug reactions caused by the anti-epileptic drugs.

MATERIALS AND METHODS

Study Design: Prospective Observational Study
Location Of Study: General Medicine, OGH, Tertiary care teaching hospital
Study Period: 6 Months
Study Population: All patients attending with epileptic seizures
Sample Size: 104
Selection Criteria:

Inclusion Criteria	Exclusion Criteria
Patients of all age groups who were prescribed AED's.	Pregnant women
	Patients with sleep disorders and those in-patients in which Benzodiazepine derivatives were prescribed for sedation purpose.

Procedure for Data Collection and Analysis:

In a prospective study spanning six months (December to May 2016) we collected and analyzed the prescription data of 104 patients of seizures from neurology Out Patient department (OPD) and the General Medicine Department of Osmania General Hospital, Hyderabad.

Data collection for patients was done through demographics, admission notes, past medical history and patient's attender. Diagnosis and medications prescribed was recorded from daily reviews of clinicians' notes and treatment charts respectively. For all epileptic patients a documentation form was designed and interviews by prescribing clinician, patients and/or by their attendant where necessary.
The demographic data, diagnosis, type of seizures, the anti-epileptic drugs prescribed and the adverse drug reactions (ADRs) reported by the patients were recorded.

RESULTS

Of the 104 seizure cases, nearly half 58 (55.76%) belonged to productive age group (15-45 years). Almost 2/3rd of cases, i.e., 69 (66.34%) were males and 36 (33.66%) were females. Mean age of the subjects was 30.97 years (SD = 18.9 years). Mean duration of seizures was 6.3 years (SD = 8.3 years) and median duration was 3 years. Mean number of episodes was 4.5 (SD = 8.3). 86.7% cases were unskilled workers and 82.9% cases belonged to low socio-economic status [Fig5]. Family history of

seizures was present in 19 (18.26%) out of 104 cases. Mean age of onset of seizure was 19.9 ± 18.8 years. Age of onset was below 20 years in about 1/3 (35) of cases (33.65%). Proportion of generalized tonic clonic seizure (GTCS) cases was 80 (78.8 %).

Prescribing indicators:

1) Average number of anti-epileptic drugs (AEDs) prescribed per patient. This is calculated as: Average. no. of AEDs/patient = 159.37/104 = 1.5324

2) The types of seizures encountered in this study and their frequency are shown in Fig No.01.Among all seizure types, idiopathic generalized epilepsy were accounted for 76.9% followed by symptomatic epilepsy seizures (26.9 %).

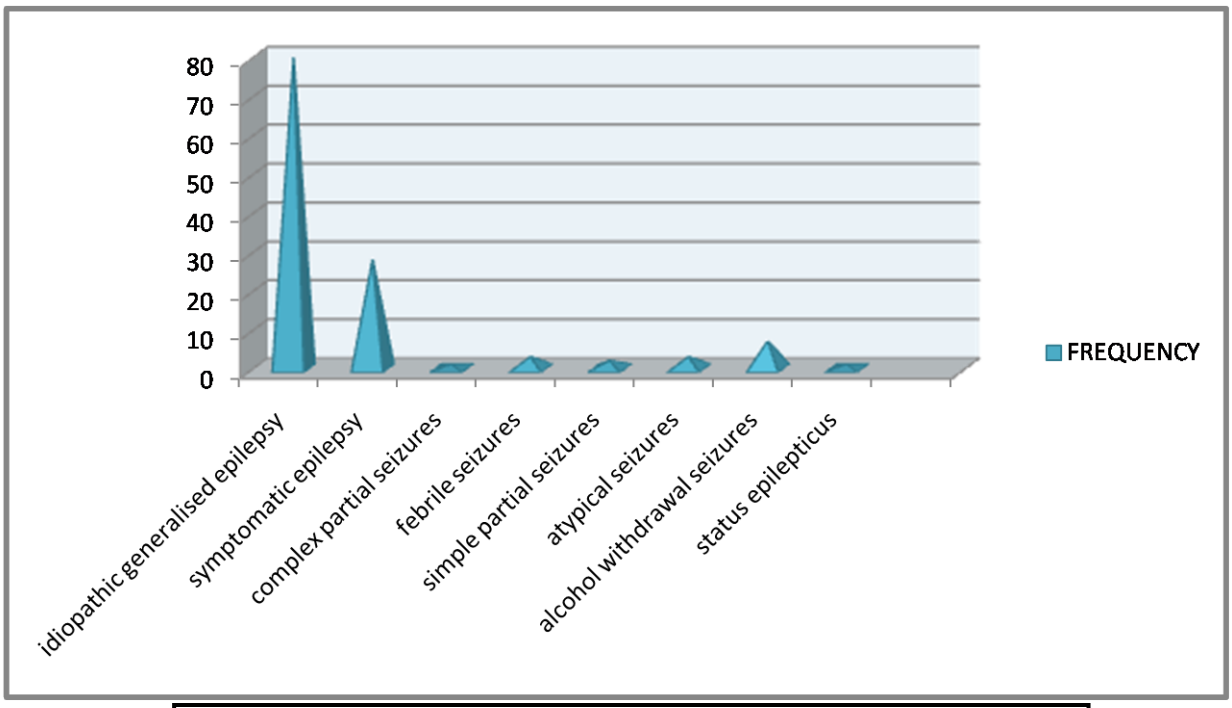

Fig No. 01: SEIZURE TYPES AND THEIR FREQUENCY

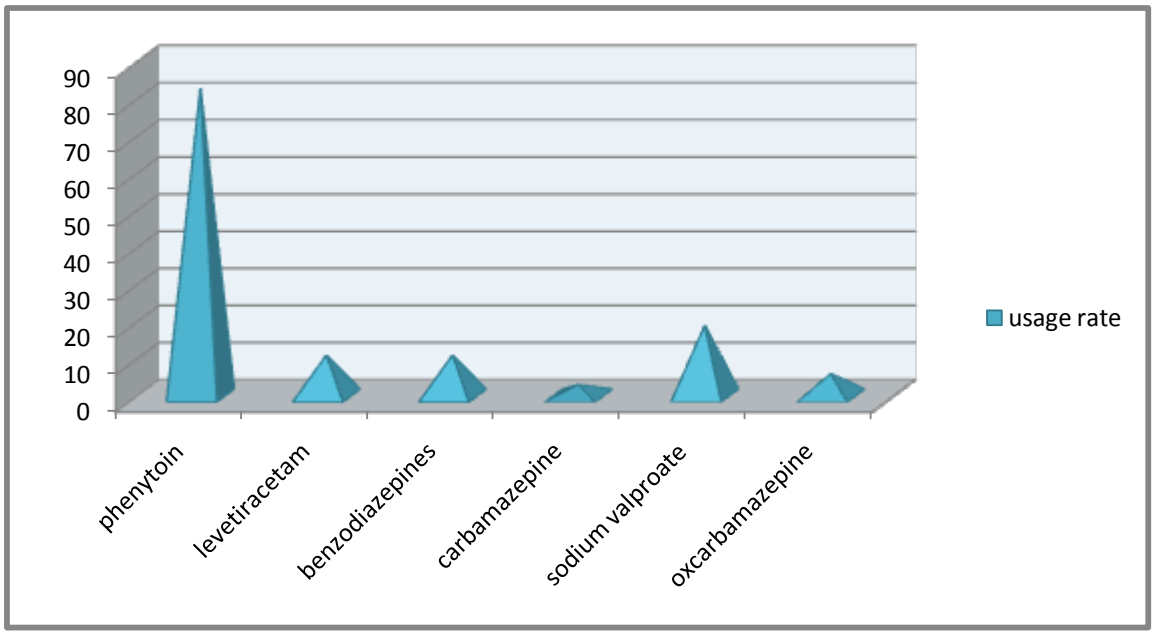

Fig No. 02: USAGE RATE OF ANTI-EPILEPTIC DRUGS

The most commonly prescribed anti-epileptic drugs (AEDs) in our study were Phenytoin 58.86% followed by Sodium Valproate 13.47%. The drug(s) prescribed in each type of seizure is shown in Fig No. 02. Phenytoin was the most common drug used 83 (58.86%) followed by levetiracetam 19 (13.47%). Other commonly used drugs were benzodiazepines 11 (7.80%), Carbamazepine 3 (2.12%), and Sodium Valproate 11 (7.80%), oxcarbamazepine 6 (4.25%) . Out of 104 seizure cases, 43 (41.3%) patients were compliant with the AEDs.

3) Incidence Of Mono And Polytherapy (Fig No.03).

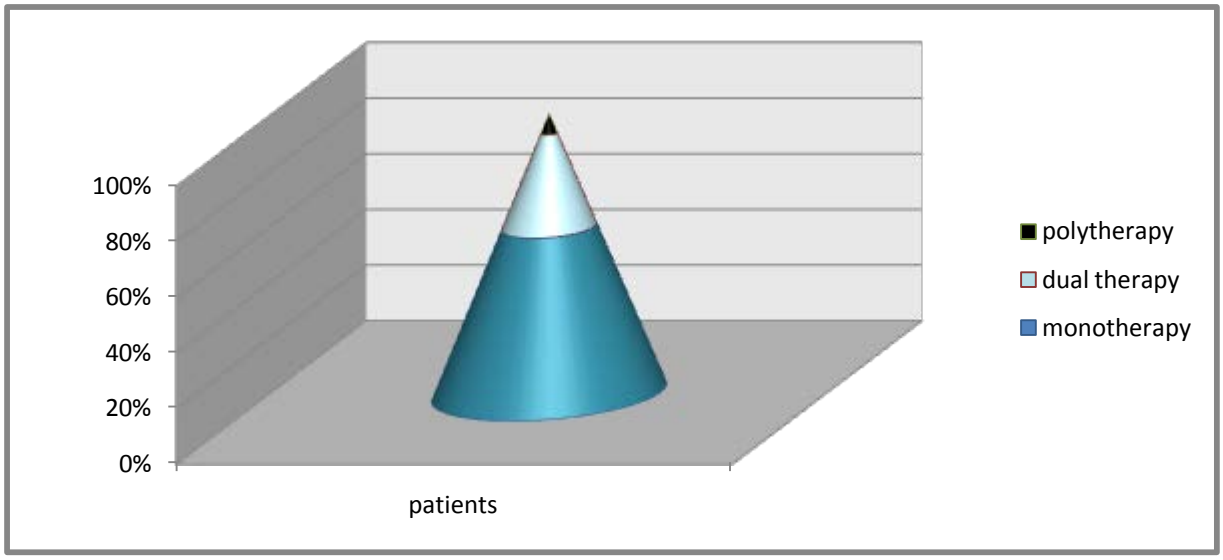

Fig No. 03: INCIDENCE OF MONO AND POLYTHERAPY

Patient indicators:

1) Total number of patients in the study = 104

a) Number of male patients = 69 (66.34%)

b) Number of female patients = 36 (34.61%)

2) Age range of patients = 15 years to 70 years.

a) Average age of male patients = 41.75 years.

b) Average age of female patients = 27.3 years.

Age and sex distribution of seizure cases:

Nearly half (55.76%) of the 104 cases belonged to productive age group (15-45 years) and 2/3rd (66.34%) were males.

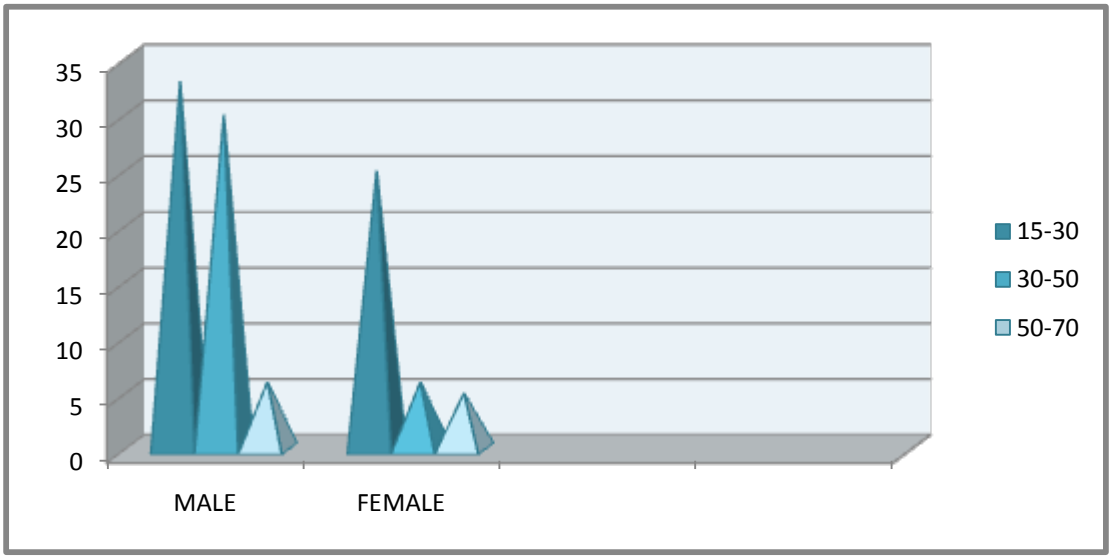

Fig No. 04: AGE AND SEX DISTRIBUTION OF SEIZURE CASES

Socio-economic status of seizure cases (*n*=104):
Majority (>60% cases) were unskilled workers and of low socio-economic status groups.

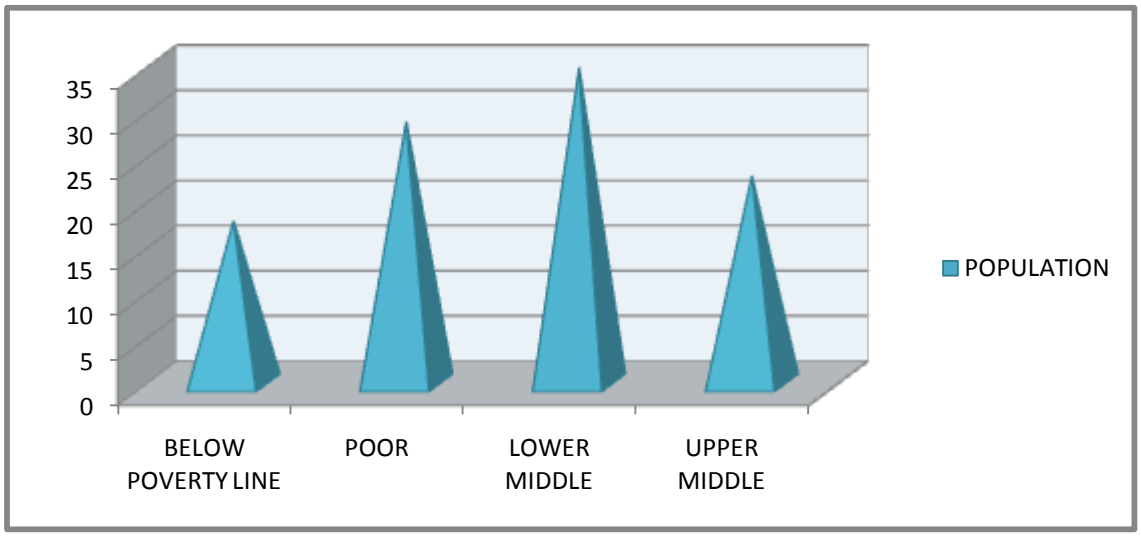

Fig No. 05: SOCIO-ECONOMIC STATUS OF SEIZURE CASES

Age of onset among seizure cases:
Of the 104 seizure cases, nearly half 58 (55.76%) belonged to productive age group (15-45 years). Almost 2/3rd of cases, i.e., 69 (66.34%) were males and 36 (33.66%) were females. Mean age of the subjects was 30.97 years (SD = 18.9 years).

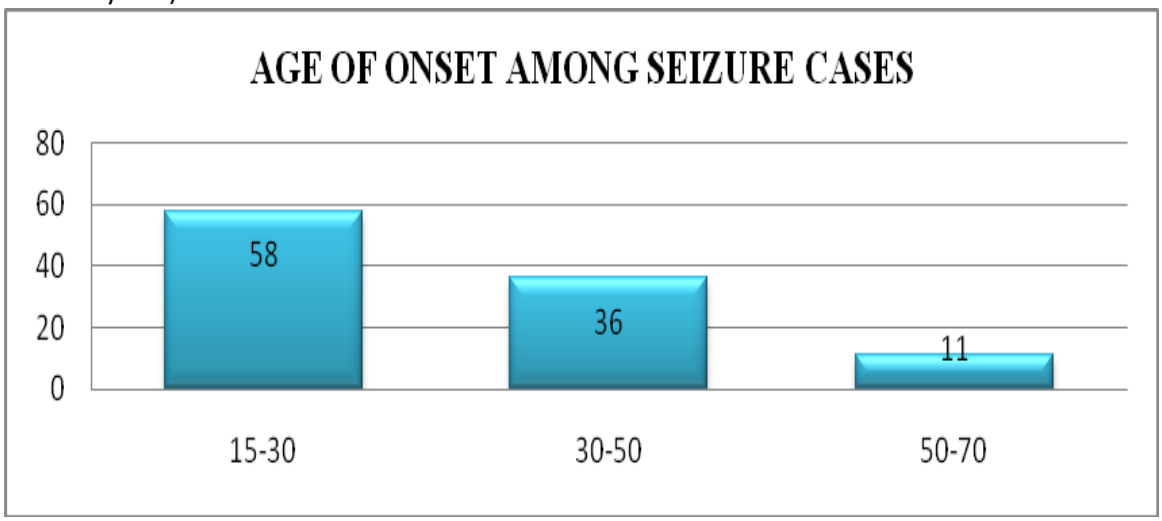

Fig No. 06: AGE OF ONSET AMONG SEIZURE CASES

Clinical features seen significantly more among GTCS was up-rolling of the eyes followed by urinary incontinence and salivation. In cases of ordinary partial seizures salivation was the most common clinical presentation, whereas in tonic seizures it was cyanosis. Among cases of absence seizures it was day dreaming. Causes of seizures were idiopathic in 76 (73.07%) cases and secondary in 28 (26.92%) cases. The most common causes of secondary seizures were alcohol addiction 11 (10.57%), head trauma 7 (6.73%), stroke 6 (5.76%) and drug withdrawal 5 (4.80%). The other causes were fever 3 (2.88%), neurocysticercosis 1 (0.96%), meningoencephalitis 1 (0.96%).

Among the associated disease conditions, diabetes mellitus was present in 20 cases, hypertension in 13 cases, human immunodeficiency virus infection in 2 cases, behavioral abnormalities in 11 cases, mental retardation in 8 cases, loss of memory in 5 cases and depression in 9 cases. All cases with behavioral abnormalities presented with GTCS. Mental retardation was associated with 8 cases, 6 of which presented with GTCS and one case each as atypical and complex partial seizures. Out of the 5 cases with the loss of memory, 4 had GTCS and 1 had complex partial seizures. Out of 9 cases with depression, 4 had GTCS, 2 had simple partial seizure, 2 had atypical seizure and 1 had focal seizure.

History of status epilepticus was present in 1 (0.96%) cases. Drug administered for management of this condition was sodium valproate, diazepam and clonazepam.

Alternate system of medicine for case management was carried out in 6 (3%) cases. Of this, 4 patients (3 with GTCS and 1 with absence seizures) had taken ayurvedic treatment and 2 (both with GTCS) had taken homeopathic treatment.

Monotherapy regimen was seen significantly more in all types of seizures except focal where two drug therapies with AEDs were more commonly used [Fig No. 07].

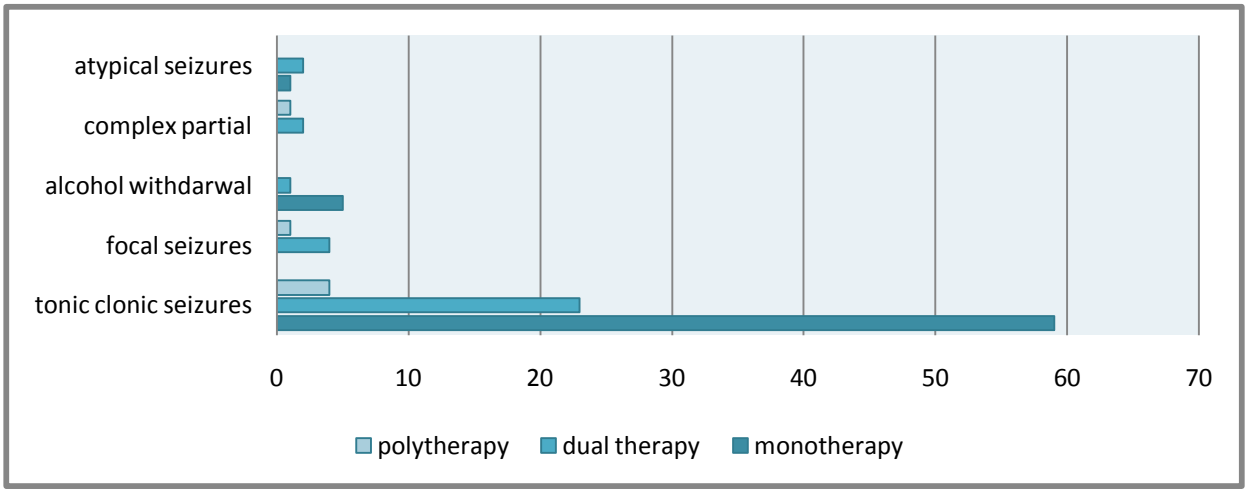

Fig No. 07: RELATION BETWEEN TYPES OF SEIZURES AND TYPES OF DRUG REGIMEN

Adverse drug reaction (ADR) profile: 6 patients out of a total of 104 reported ADRs (incidence = 5.769%) .Phenytoin and Carbamazepine contributed equally to the occurrence of adverse effects (six cases each). None of the patients received any treatment for adverse effects.

- **TEN(Toxic Epidermal Necrolysis) Secondary To Phenytoin Use** (Papulae Rash On The Right Elbow Which Progressed To All Over The Body Causing Discoloration And Desquamation) - **Naranjo Score 5 (Probable ADR)**
- **SJS Progressed To TEN (Phenytoin Induced)** (Wide-spread Blistering Exanthemas of Macules Around The Lips And Neck) - **Naranjo Score 7 (Probable ADR)**
- **Phenytoin Induced Erythema Multiforme** (Generalized maculopapular rash in accordance with erythema multiforme major after introduction of phenytoin) - **Naranjo Score 6 (Probable ADR)**
- **Phenytoin Induced Oral Erythema Multiforme** (Irregular Lip Ulcerations With Blood Encrustations) - **Naranjo Score 3 (Possible ADR)**
- **Phenytoin Hypersensitivity Syndrome** (Hemorrh-agic Crusting Of Lips In Phenytoin Hypersensitivity Syndrome) - **Naranjo Score 6 (Probable ADR)**
- **Phenytoin Induced Hypersensitivity** (Erythemato us, Eroded Areas Involving The Face, Neck And Upper Chest) - **Naranjo Score 6 (Probable ADR)**

DISCUSSION

In this study, idiopathic generalized epilepsy was the commonest type of epilepsy 73.07% and phenytoin was the commonest drug prescribed 58.86% for its treatment, followed by sodium valproate 13.47%.

Symptomatic epilepsy comprised the second commonest category of seizures 26.92%. It included seizures due to structural lesions of the brain such as stroke, cerebral bleed, trauma, cerebral atrophy, tumour etc. Phenytoin 86.20% followed by levetiracetam 37.93% was the most commonly prescribed drugs. Phenytoin was widely prescribed in our study, unlike another South Indian study by Radhakrishnan et al (2000). where it was underutilized, inspite of being less expensive.

Simple febrile seizures were treated with diazepam in the acute stage and therapy was maintained with Clobazam. The latter drug is preferred as maintenance therapy to prevent recurrence. It has fewer side effects like ataxia and drowsiness compared to Diazepam and also ensures better patient compliance. In cases of complex febrile seizures Diazepam/ Phenytoin/ Sodium Valproate were used in the acute stage and Clobazam was used for maintenance therapy.

Among the newer AEDs levetiracetam was most commonly used as an adjuvant drug. It was most often combined with phenytoin (12 cases) followed by combination with valproate (four cases), Oxcarbazepine (three cases) and carbamazepine (one case). Unlike a study at DCMS ShobhanaMathur et al. which recorded frequent use of newer AED namely Topiramate as an adjuvant. levetiracetam was the commonest adjuvant drug and recorded maximal use in generalized tonic clonic seizures (breakthrough). Though the efficacy of levetiracetam is similar to the conventional drugs, it was preferred because of lesser incidence of adverse effects. In contrast to other studies, our study revealed frequent use of newer AED levetiracetam.

In case of partial seizures (both simple and complex) (3 cases) Carbamazepine was used as first line drug in only one case and other two cases were managed by phenytoin and oxcarbamazepine with levetiracetam being their common adjuvant. Standard treatment guideline demands use of carbamazepine as first line drug in management of partial seizure.

The overall incidence of adverse drug reactions (ADRs) was about (6 patients out of 104 i.e. 57.69%) when compared to another study conducted in hyderabad at Deccan college of medical sciences(4.67%) shobhanamathur et al (2010).

A recent meta-analysis study showed that the age-specific prevalence rates were higher in the younger age group, with the onset of epileptic seizures reported mostly in the first three decades of the sample population's lives .Mean age of onset of epilepsy in a study conducted by Thomas SV et al., (2001) was 14.8 years in contrast to our study which is 30.97 years. Studies carried out in Jaipur, by Sridharan R &Murthy BN et al.,(1999) and Kollar B et al.,(2009) showed that the sex ratio (Male : Female) was 2:1 and a high proportion of cases (62.83%) were from low socio-economic group which was similar to our findings. As younger age group and people of poor socio-economic group are more affected by this condition economic deprivation in the family could be more grievous. Family history of epilepsy in a study carried out in Sudan by Hussein A et al., (2007) was present in 20% cases, which were higher than our observations. However the proportion of seizure cases due to secondary causes in the Sudan based study was same as that of ours. Hence if measures are taken to correct these underlying factors we can avoid almost a third of seizure cases in the future.

Head trauma followed by (CNS) central nervous system infection and alcohol consumption were the most common cause of secondary epilepsy in this study. However, the study carried out in Sudan by Hussein A et al.,(2007) reported cerebrovascular accidents (10%) followed by CNS infections like meningitis or encephalitis (5.9%) and previous history of head trauma and alcohol consumption (each in 4.2% cases) as the most common cause of secondary epilepsy. A community based study carried out in Kerala state of India by Radhakrishnan K et al.,(2000) showed that the proportion of generalized and localization-related epilepsies was 58.8% and 30.6%, respectively.In contrast, another study carried out in Eastern India by Sil A et al.,(2012)showed that 81% seizure cases were GTCS, 17.7% partial and 1.3% myoclonic seizures. The varying proportion of cases may be due to the difference in the pattern of admission or referral services.

A study done in Jaipur by Panagariya A et al., (2012) and Sudan by Hussein A et al., (2007) found that EEG was abnormal in 58.9% and 64.8% epilepsy patients, which were higher than our findings. CT was abnormal in 33.5% cases in Jaipur based study similar to our findings, but the Sudan based study found it in 16.7% cases, which was lower than our observations.

The non-compliance rate of 25.8% and the finding that patients on monotherapy were significantly more compliant (95.3%) than patients on polytherapy (77.8%) as reported in Burdwanstudy by Sil A et al.,(2012), was similar to our findings. There is a need to minimize noncompliance rate by educating patients about the importance of adherence with AEDs even during periods of normality to avoid recurrent attacks. Probably use of monotherapy would help in minimizing non-compliance as supported by the observations in this study. A meta-analysis study found that the treatment gap was more than 70% in the rural areas. Furthermore, studies done in most (SEAR) South East Asian Region member countries has revealed that nearly 50 to 80% of people with epilepsy do not receive systematic treatment and among those who are on treatment, nearly 40% to 70% drop out at various stages of treatment resulting in the recurrence of seizures[25]. In view of the above findings, it is insisted that proper diagnostic techniques, supervision and follow-up of patients are crucial parameters required for quality improvement of services of this group.

CONCLUSIONS

Idiopathic generalized epilepsy was the commonest type of epilepsy recorded. Monotherapy was preferred in most cases. Unlike previous studies Phenytoin was the most frequently prescribed AED followed by Sodium Valproate. In contrast to other studies, our study revealed frequent use of newer AED namely levetiracetam.

Nearly half of the cases belonged to productive age group (15-45 years) and 2/3rd were males. Majority (>60% cases) were unskilled workers and of low socio-economic status groups. Family history of seizures was present in 18.9% cases. Mean age of onset of seizure was found to be 28.32 years.

In view of the above findings, it is insisted that proper diagnostic techniques, supervision and follow-up of patients are crucial parameters required for quality improvement of services of this group. Seizure manifestations and treatment compliance vary widely in the studied population. In depth analysis of each seizure type will give more information about the factors associated with it.

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