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Original Article

Drug Utilization Evaluation of Anti Epileptics used in Guntur City Hospital

Sk. Sulthan Shaheed [1,*], V Satyanarayana [2], J N Suresh kumar [3], CH Siva Rama Krishna [4]

[1] V Pharm.D Student, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt), Andhra Pradesh, India-522601.

[2] Department of Pharmacy Practice, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt), Andhra Pradesh, India-522601.

[3] Department of Pharmaceutics, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt), Andhra Pradesh, India-522601.

[4] Department of neurology, Guntur city hospital, Guntur (Dt), Andhra Pradesh, india.

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ABSTRACT

Introduction: Epilepsy is a common medical condition characterized by repeated seizures due to a disorder of the brain cells. the data was limited regarding the prescribing pattern and side effects of various anti epileptic drugs in various population. The aim of present study was to evaluate the effective use of anti epileptic drugs in the management of various types of epileptic seizures over a period of six months. **Materials and methods:** A prospective observational study was conducted among epileptic patients on follow up at neurology department of Guntur city hospital. During the six months study period, epileptic patients who were prescribed with AED's (Anti Epileptic Drugs) were in this study. Data were collected through the hospital medical records. **Results:** A total 150 patients included in this study, in this n:89 (57.33%) were males, 61 (40.66%) females. The most common type of seizures diagnosed as generalised Tonic Clonic seizures 108 (72.0%) effected with GTC's, males 62 (57.40%), females 46 (42.59%) partial seizures 22 (14.66%). Mono therapy commonly used in the treatment of epilepsy 97 (64.66%), dual therapy 41 (27.33%) poly therapy 12 (8.0%). Among which new anti epileptic drugs levetiracetam was the most commonly utilised single drug and multiple anti epileptic drug followed by Valproic acid, Carbamazepine, and Phenytoin. In this study 52 adverse drug reactions are identified.
Conclusion: This study highlights the need of drug utilization evaluation and therapeutic drug monitoring of epileptic patients. Improving the rational use of anti epileptic drugs like Levetiracetam, Lamotrigine, Topiramate etc. Most of the ADR's are mild and predominant in females.

Key words: Epilepsy, Adverse drug reactions, Rational drug use, Drug utilization and evaluation.

1. INTRODUCTION

The word epilepsy comes from the Greek and means to be taken, seized or attacked. Epilepsy is a condition characterized by repeated seizures due to a disorder of the brain cells.[1] epilepsy is more common in the developing countries than developed countries. In developing countries

Corresponding author *
Mr.V. Satyanarayana M.Pharm(Ph.D)
Assistant Professor, Department of Pharmacy Practice ,
Narasaraopeta Institute of Pharmaceutical Sciences,
Narasaraopet, Guntur(D.t), A.P. India-522601.
E-mail: veeragandamsatya@gmail.com

the prevalence has been reported to be more than 40 per 100 population.[2] In india 10 million peoples effected with epilepsy (prevalence about 1%).[3] the incidence high in rural area (1.9%) as compared with the urban areas (0.6%).[4,5]

Now a days the pharmaceutical industries develops newer type of AED's. These drugs are mainly used to controlling epilepsy. Single drug therapy or combination of other drugs. Mainly mono therapy was used to treat the epilepsy.[6] the risk of epilepsy varies individual patient. There is a risk of having epilepsy 2-5% in their life span.[7]

The seizure attack may vary person to person and the type of seizures. It occur anytime, anywhere, with or without warning. At the time of seizures may produce injury and severe condition even death of the person.[8]

The causes of epilepsy also different person to person. It includes genetic predisposition for certain seizures, Head Injuries, Brain Infections, Brain tumours, Stroke, Smoking And Alcohol, Drug withdrawal etc.[9,10] seizures are divided mainly into two types partial and generalised seizures. The epilepsy was diagnosed by using Electroencephalogram (EEG), Computer Tomography (CT), Magnetic Resonance Image (MRI) of brain, symptomlogy.[11] The ultimate goal of the treatment was minimizing the side effects of the drugs, improving the quality of the life.

Various factors effecting the drug treatment like the type of epilepsy, age, gender of the patient, availability of the medication and side effects of the drugs. Based up on genetic, environmental, pharmacodynamic and pharmacokinetic in different racial groups the drug response effectiveness may vary. The side effects, ADR's mainly produces by using the drugs to treat epilepsy due to the long duration of treatment and multiple drug therapy.[12]

The plasma concentration of the AED's provides information regarding the reduction of seizures or side effects. The treatment outcome depends up on the drug related factors, disease related factors and patient related factors, sudden withdrawal of drug increases the seizure frequency and severity.[13,14]

Epileptic patients in developing countries are not taking appropriate treatment due to lack of education, poor financial status, limited access of services, poor health care system in adequate supply of AED's.[15] These factors are essential to study the utilization pattern of anti epileptic drugs and ADR's, controlling of epilepsy by improving clinical pharmacy services. So our aim was to evaluate the effective use of anti epileptic drugs in neurology department of Guntur city hospital.

2. MATERIALS AND METHODS

Study site and population:

This prospective observational study was conducted at inpatient and outpatient department of Guntur city hospital is a 250 bed hospital. This study was carried out over 6 months period (from July 2016 to December 2016) during which the prescription data of 150 patients were acidited objectively. All patients (In and out patients) who were prescribed with anti epileptic drugs (AED's) were considered for analysis.

Identification of patients:

Data from patients admitted or visit to the hospital during July 2016 to December 2016 were included in the study. Out patients and emergency patients were identified through pharmacy drug, clinical pharmacist using the wards registers.

Data source and data collection:

Patient age 10 yrs and above with seizure disorders who were follow up for at least one year from the last AED's added And had a complete set of desired information (patient identity age, sex, occupation, comprehensive clinical history associated disorders, examination findings, investigation reports and the drug usage profile with any adverse event) in record files were included in the study.

Data collection:

A questionnaire was used to take data regarding demographic (age and gender), admission notes, past medical history, type of seizures, age of onset of seizures, frequency of seizures at onset, type and aetiology of epileptic seizures AED's data (name of the AED's, mono or poly therapy, no of AED's per prescription, formulation) and at the end of the follow up at GCH (Guntur City Hospital), clinical or biochemical evidence of any ADR's.

Diagnosis and medications prescribed were recorded from daily reviews of clinician's notes on the information on diagnosis and or intended purpose for AED's use.

The epilepsy clinic used simple 1981 international league against epilepsy (ILAE) classification system to label the seizure events in record file (commission on classification and terminology of the international league against epilepsy, 1981)

The epileptic seizures were grouped according to the classification of the international league against epilepsy. So we grouped seizure events simply as partial (complex partial, simple partial, secondary generalised (Generalised tonic- Clonic, Absence, Myoclonic, Clonic, Tonic, Atonics).

Data collection information:

- **i)** **Patient demographic details**
  - ➢ Age
  - ➢ Gender
  - ➢ Weight
  - ➢ Social status
  - ➢ Marital status
- **ii)** **Seizures history**
  - ➢ Age of onset of seizures
  - ➢ Duration of seizures
  - ➢ Type of seizures
  - ➢ Duration of therapy
  - ➢ Seizure frequency at the end of follow up
- **iii)** **Risk factors of seizures**
  - ➢ Family history
  - ➢ Head injuries

1530

- Brain infections
- smoking / alcohol consumption
- stress, stroke

iv) Complications of seizures
- Stroke
- Injuries
- Accidents
- Status epileptics

v) Drug related information:
- No of AED used
- Dose of AED at every visit
- Dose of AED'S
- Changes in frequency of seizures

vi) Medication therapy management
- Changes in blood picture
- Skin reactions
- Gastrointestinal tract (GIT)
- Central nervous system (CNS)
- Liver abnormalities

Inclusion criteria:
- Patients with seizures, of both sex and all age groups, who are prescribed an anti epileptic medication.

Exclusion criteria:
- Pregnancy women, Lactating mother
- Patients with other CNS disorders

Data quality:
The collected data were thoroughly reviewed by academic clinical pharmacist To maintain the quality of data. Tran scripted data were also reviewed against data collection Performa to minimize transcription error's.

Anti epileptic drug with effectiveness and tolerability profile:
Drug related data included the AED's regimen at initial visit and at the end of follow up along with and ADR's. Treatments were provided by experienced neurologist in the clinic. They also recorded any adverse drug reaction either reported by the patient or found through routine examination and investigation during follow up. Tolerability was measured by extracting data from the record files on the known ADR's (Anaemia, TCP, and Skin rash, Gastro-intestinal, Liver, and CNS) of the drugs.

Statistical analysis:
The collected data were cleared, categorised and analysed using statistical package for the social sciences (SPSS) version 20.0 for Microsoft window, and the results were presented in tables and figures as necessary. Descriptive analysis was used to describe the percentage and number distribution of variables.

Ethical considerations:
The study protocol was approved by the ethical review committee of the Guntur city hospital. All data obtained in the course of the study were kept confidential, and used solely for the purpose of the study.

3. RESULTS

Patient Demographic characteristics:
A total 150 patients were included in this study over 6 months period (from July 2016 - December 2016). Seizures were more common in males. The demographic data revealed that the number of male and female patients were 89 (59.33%) and 61 (40.66%) respectively, among these 11-20 and 31-40 years age groups, are more. Prevalent that accounted 50 (33.33%) and 43 (28.66%) respectively (Table – 1 and figure-1)

Table : 1 Sex group of Epileptic patients (n:150)

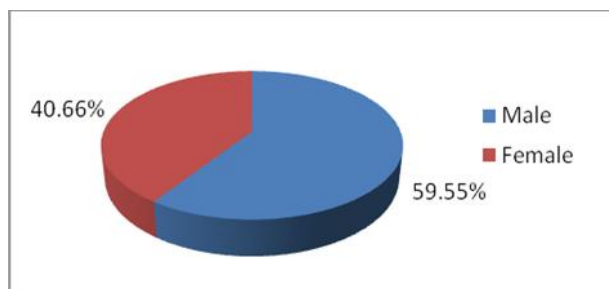| S.No.	Gender	No of patients	%
1	Male	89	59.55%
2	Female	61	40.66%

Fig 1: Shows Sex Group of Epileptic Patients.

Classification and Treatment of Seizures :
In our study total 150 patients 128 (85.33%) were having generalised seizures, 22 (14.66%) patients were having focal seizures. Generalised Tonic Clonic seizures were the most prevalent of all types of epileptic seizures which accounted in 72% of patients followed by partial seizures 13.33% in adult patients (Table – 2,3 and figure-2) status epileptics in 0.66% patients. Idiopathic epilepsy was the most common cause of epileptic seizures 7.33% in adults. The idiopathic seizures include various epileptic syndromes like dress syndrome etc.

Table: 2 Classification Of Epileptic Patients Based Up On Gender (n:150).

Type Of Seizure	Male	Female	No	%
Generalized seizures:	62	46	108	72
GTC's	1	1	2	1.33
Absence	4	1	5	3.33
Tonic	1		1	0.66
Myoclonic				
Partial seizures:	2	0	2	1.33
SPS	14	6	20	13.33
CPS	1	0	1	0.66
Status epileptics	5	6	11	7.33
Un classified/ idiopathic				

GTC's= Generalised Tonic Clonic seizures, SPS= Simple Partial seizure, CPS= Complex partial seizure.
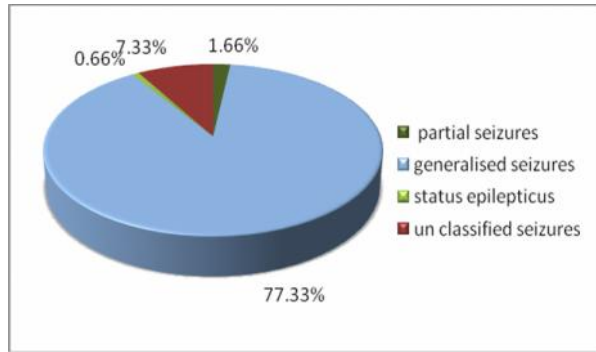
Fig 2: Classification Of Seizures

Table: 3   Mode Of Epileptic Treatment Used Based Up On Age (n:150).

Age	Single drug	Dual drug	Triple drug
1-10	8	1	1
11-20	32	13	5
21-30	27	14	2
31-40	13	3	2
41-50	5	5	1
51-60	2	5	0
61-70	1	0	1
71-80	0	0	0

Over all utilization of AED's in patients:

In this study population, 97 (64.66%) were prescribed an AED as mono therapy and 41 (27.33%) needed dual therapy. 12 (8.0%) patients were managed with poly therapy (3 AED's). most of the poly therapy prescribed consisted of poly therapy. only one patient were administered with four AED's.

Mono therapy was used in 97 (64.66%) epileptic patients most frequently used AED's as mono therapy in Generalised seizures. Levetiracetam (N:37   24.66%), and Valproicacid n:23 (15.33%), Carbamazepine n:21 (14%), Phenytoin n:11 (7.33%), Phenobarbital 5 (3.33%), where as Levetiracetam 7 (4.66%), Phenytoin 5 (3.33%), Carbamazepine 8 (5.33%), Valproicacid 2 (1.33%) was the most common AED's used in mono therapy of generalised seizures. Utilization pattern of different AED's mono therapy in different type of seizures are highlighted in (Table 4 and figure-3).

Table: 4 Classification Of Epileptic Seizures And Mode Of Treatment (n:150).

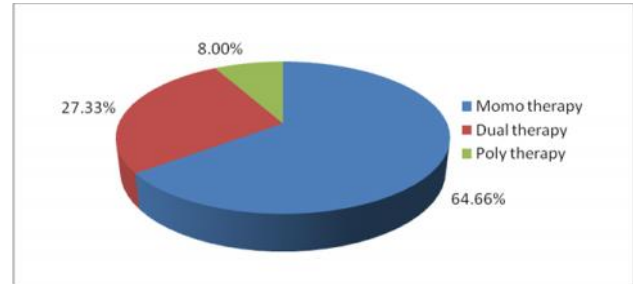| Type of seizures	Mono therapy	Dual therapy	Poly therapy	No	%
Generalized seizures:	72	26	10	108	72
GTC's	2		0	2	1.33
Absence	2	3	0	5	3.33
Tonic	1		0	1	0.66
Myoclonic					
Partial seizures:	0	2	0	2	1.33
SPS	13	6	1	20	13.33
CPS	1	0	0	1	0.66
Status epileptics					
Un classified/ idiopathic	6	4	1	11	7.33

Fig 3: Mode of Treatment Used For Treating Epilepsy

Combination of AED's:

The most frequently used combination therapy of AED's consisted of PHT/VPA n:6 (4%), CBZ/VPA n:2 (1.33%), LVA/CBZ n:13(8.66%), LVA/PHT N:13(8.66%), PHT/CBZ n:4 (2.66%) (Table:5)of the prescribed drugs are from the Essential drug list(EDL).

Gender specific distribution of AED's:

The utilization of all AED's high in males compare to female. Levetiracetam and Carbamazepine is find to use more often in women than men. Levetiracetam, valproicacid as found to use more in males than females.

Table: 5 Over All Utilization Of AED's In Epileptic Patients (n:150)

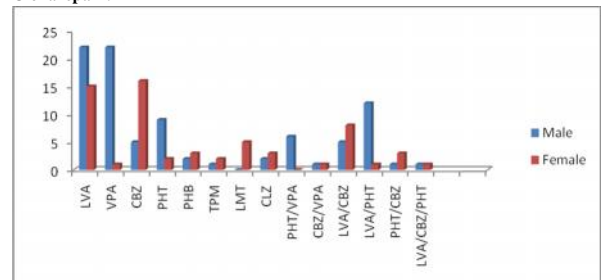| Drug	male	Female	No	%
LEV	22	15	37	24.66
VPA	22	1	23	15.33
CBZ	5	16	21	14
PHT	9	2	11	7.33
PHB	2	3	3	2
TPM	1	2	5	3.33
LTG	0	5	5	3.33
CZP	2	3	2	1.33
PHT/VPA	6	0	13	8.66
CBZ/VPA	1	1	13	8.66
LEV/CBZ	5	8	4	2.66
LEV/PHT	12	1	2	1.33
PHT/CBZ	1	3		
LEV/CBZ/PHT	1	1		

Fig 4: Shows over All Utilization Of AED's in epileptic patients.

Adverse effects of (AED's):

In our study group 150 patients developed 52 ADR's of various types (Table-6, figure-5) some patients developed more than one ADR's the organ system affected was GI system and CNS. The most ADE's mostly causes Anaemia n:6 (11.53%), Rash, Utricaria, SJS n:7 (13.4%), Gum Hyperplacia n:2 (3.84%), GI Disturbances n:10 (19.23%), Headache n:11 (21.15%), weak ness n:8 (15.38%), Anxiety n:10 (19.23%). The most common drugs causes for ADR's were Phenytoin n:20 (38.46%), Valproicacid n:12 (23.07%), and Carbamazepine n:18 (34.61%), Levetiracetam n:2 (3.84%). The ADR's assessed by using WHO probability scale and Naranjo's algorithm respectively. In our study it is observed that mild type of adverse drug reactions 28 (53.84%), moderate type of adverse drug reactions 14 (26.92%), severe type of ADR's 10 (19.23%) (Tab'le-7,figure-6). All this reactions Medications were discontinued in 10 cases and the dose was altered in 14 cases due to the ADR's are severe and moderate. . The drug was not changed in 28 cases due to the ADR's are mild.

Table 6: Adverse Drug Reactions (ADR's) with AED Mono therapy

Type of reaction	CBZ	VPA	PHT	LEV
Anemia, TCP	3	1	2	0
Rash, Utricaria, SJS	2	2	1	2
Gum hyperplasia	0	0	2	0
GI Disturbances	5	3	2	0
Headache	4	2	5	0
Weakness	2	1	4	0
Anxiety	3	3	4	0

TCP: Thrombocytopenia, SJS: Steven john son's syndrome, LEV: Levetiracetam,CBZ: Carbamazepine, VPA: Valproicacid, PHT: Phenytoin.
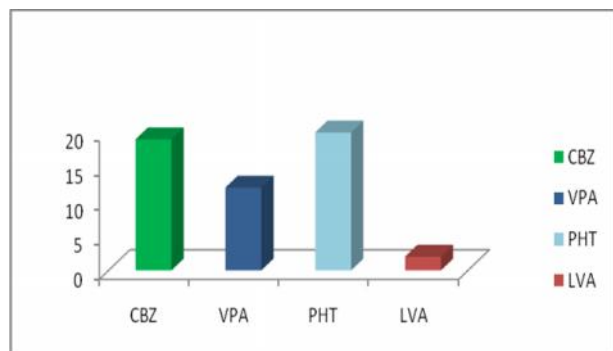

Fig 5: Shows ADR's Produced By AED's Mono Therapy.

Table 7: Severity Of ADR's Produced By AED's

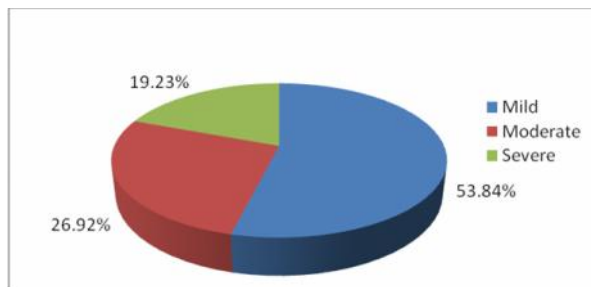| Type of ADR's	No	%
Mild	28	53.84
Moderate	14	26.92
Severe	10	19.23

Fig 6: Shows Severity of ADR's

4. DISCUSSION

There is increase in refractory epilepsy and serial epilepsy and also increase side effects related to older AED's due to this the pharmaceutical Industries develops newer AED's. Data available regarding the therapeutic efficacy of these drugs and mono therapy versus combination therapy for management of seizures disorders are scant but there are no significant advances and extensive studies regarding the therapeutic monitoring and proper pharmacovigilance for AED's.

In this present study of drug utilization and evaluation of AED's, a total no of 150 epileptic patients were included. According to this study result, GTC's was the most common type of epileptic seizure 72% in our study we found that the incidence of epilepsy in males 59.33% were greater than females 40.66% which is accordance with some previous findings.[16] some studies supported incidence of epilepsy was high in male.[17] in some other studies they described the female predominance over male.[18,19]

The most common type of seizure was generalised tonic clonic seizures 72% which was the most common followed by complex partial seizures (13.33%). In developing countries central nervous system infections are one of the cause of producing epilepsy. In our study we found that Granuloma with seizure 12 (8.0%), Calcification with seizures 21 (14%), Lacunars infract 6 (4%).

In our data indicated that mono therapy followed by dual therapy was the therapy of choice in majority of patients with partial or generalised seizures. In most of the epileptic patients respond to one of the first line AED's. If the patient not respond to mono therapy in this condition dual therapy or combination of drugs are mainly used.

In this study, newer anti epileptic drug Levetiracetam was mainly prescribed to the patients due to the reducing the side effects of the drugs, followed by Valproicacid and Carbamazepine. The best AED therapy is dependent on optimal seizure control and absence of un acceptable side effects.[20] poly therapy may increases the drug – drug interactions and increases the chronic toxicity and also the cost of the treatment.

To reducing the drug-drug interactions and side effects monotherapy was mainly used. In our study, mono therapy (27.33%), in our study, Levetiracetam was the most frequently prescribed mono therapy, followed by Valproic

1533

acid and Carbamazepine. In this study it is observed that the anti epileptic drug Levetiracetam was mainly prescribed to the patients. In this study Levetiracetam was the commonest AED used in mono therapy or combination therapy, followed by Valproic acid and Phenytoin and Carbamazepine. By using poly therapy there is no use compare to using mono therapy.[21] poly therapy may increases the risk of chronic drug toxicity and it may increases the cost of medication. Therapeutic drug monitoring of drugs was essential in prescribing poly therapy to epileptic patients.[18]

In our study 52 ADR's are identified the data was collected by questioning the patient directly. In 52 patients observed side effects. Headache was the most common side effect 11 (21.15%) patients, followed by GI disturbances 10 (19.23%) patients and weakness 7 (13.46%). Severe ADR's Gingival hyperplasia due to Phenytoin 2 (3.84%), Phenytoin mainly causes GI disturbances, SJS (Steven Johnson's syndrome), Rashes, Anxiety. Valproic acid (Anaemia, TCP (Thrombocytopenia, Headache, Rashes). Carbamazepine (GI disturbances, Headache, Rashes).

A rare ADR's identified in this study. Levetiracetam produces the Psoriasiform drug eruption it is the rare ADR's two cases are identified in this study.[22] Literature was very less in this type of reaction caused by Levetiracetam. Most of the ADR's are mild drug treatment was not altered in this condition.

In this study almost 58% of patients were found to be seizures free for a consecutive 2 yrs follow up period. The anti epileptic treatment was tapers the dose either with draw AED treatment after investigating the neurone imaging and encephalography of the brain. If the seizure was not controlled in that condition drug dose was altered or changes the drug therapy.

5. CONCLUSION

There is increase in the development of newer AED's safety of new AED's compare to old drugs. The new drugs are mainly used clinically now a day. In our study GTC's was the most prominent type of seizures. The adults, middle age peoples mainly effected with epilepsy. Mono therapy was mainly used to control seizures. Combination of drugs was mainly used to control the seizures if seizures are not controlled by using mono therapy. Granuloma, calcification in brain may leads to seizures.

The AED's mainly produces the side effects therapeutic drug monitoring of these drugs are essential. The present study provides valuable data of utilization patterns of AED's that may be utilized in updating the new treatment guideline and new AED's. Improving the rational use of anti epileptics is essential for minimising the side effects of epileptic drugs and severity of epilepsy.

The aetiology of seizures in children's different compare to the aetiology of adults, The treatment also different. The ADR's incidence also high in children's. The newer anti epileptic drugs like Levetiracetam, Lamotrigine, Topiramate etc. are also used in the epilepsy. Most of the ADR's are mild and predominant in females.

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