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A Prospective Observational Study on Evaluation of Effectiveness of Monotherapy and Combinational Therapy in Epilepsy Patients

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Abstract

Background: Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behaviour, sensations, and sometimes loss of awareness. (1) By definition, epilepsy requires typically two unprovoked seizures, separated by greater than 24 hours. (2) In the past epilepsy was considered as the sacred disease in support of this view a large number of people believed that epilepsy affected people who to some extent taken hold of by demons or that the visions experienced by the epileptic people were sent by the Gods.

Material and Methods: It is a prospective observational study on effectiveness of monotherapy and combinational therapy of Anti-epileptic drugs in different age groups of patients. Patients diagnosed with Epilepsy can be prescribed with single AED and combination of AED mainly on the type of epilepsy were included in our study. Our study includes 300 population with inclusion and exclusion criteria respectively as Patients diagnosed with epilepsy, including Co-morbid conditions associated with neuro and other General medicine conditions in both in-patients and out-patients department. Categories included in the study are Children, Adults and Geriatrics of both the Genders between the age group of 1-80 years. Patients associated with risk factors and complications of epilepsy. Patients suffering from severe malignant syndromes were excluded. Pregnant women's were excluded Seizure activity was recorded by performing EEG. The effect of monotherapy and combinational therapy was analysed in epilepsy patients (N=300), 166 patients were exposed to monotherapy with three different single antiepileptic drug and 134 patients were exposed to Combinational therapy with the combination four different types of AED's.

Results: The study provides an insight on evaluation of the treatment of epilepsy and the effectiveness of monotherapy and combinational therapy of Anti-epileptic drugs in different age groups of patients. Patients of different ages i.e. from 1month to 80years of age group were considered in our study and it was found that patients from age group 25-35 were mostly suffered with epilepsy. Males were mostly affected than females. Different types of Epilepsy were observed. Medication Adherence pattern was observed in 138 patients, majority of patients has shown medium type of adherence to AEDS i.e.91patients (41.86%), and high adherence (0) was observed in 29 patients (13.34%) are in baseline. Consequently 8.28% of patients were having low adherence (0) type of adherence.

Conclusion: In our study it was found that Valproic acid (49.13%) had better outcome and a combination of phenytoin and Lorazepam (35%) had superior outcome measured against other AED's combinations, concluding the suggestion for the use of combinational therapy if initial monotherapy is unsuitable for the patient

Key Word: Epilepsy, Anti-Epileptic Drug, Monotherapy, Combinational Therapy, Medication Adherence

I. INTRODUCTION

Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behaviour, sensations, and sometimes loss of awareness. (1) By definition, epilepsy requires typically two unprovoked seizures, separated by greater than 24 hours. (2) Epilepsy may develop after a particular identifiable event (e.g., asphyxia, head injury, meningitis), in which case it is called

symptomatic epilepsy, or it may develop without any identifiable cause, and then it is called idiopathic epilepsy. [3] Not only the abnormal CNS discharges vary in site, but also in severity and extent, therefore a wide variation of clinical forms is seen. A seizure is also referred to as a convulsion, fit, or attack. However, the words "convulsion" or "fit" are usually used to refer to seizures with tonic-clonic muscle movements. [3] The main difference between epilepsy and seizure is: A seizure is the event where as epilepsy is the disease associated with spontaneously recurring seizures. [5] "Epileptic seizure" is used to distinguish a seizure caused by abnormal neuronal firing from a non-epileptic event, such as a psychogenic seizure. [4] Seizures are the main symptom of epilepsy. In fact, Johns Hopkins Medicine define epilepsy as having "two or more unprovoked seizures."[6] The etiology of epilepsy is during the neonatal period and early infancy, potential causes include hypoxic-ischemic encephalopathy, trauma, CNS infection, congenital CNS abnormalities, and metabolic disorders. Babies born to mothers using neurotoxic drugs such as cocaine, heroin, or ethanol are susceptible to drug-withdrawal seizures in the first few days after delivery. Hypoglycaemia and hypocalcaemia, which can occur as secondary complications of perinatal injury, are also causes of seizures early after delivery. Seizures due to inborn errors of metabolism usually present once regular feeding begins, typically 2 to 3 days after birth. Pyridoxine (vitamin B6) deficiency, an important cause of neonatal seizures, can be effectively treated with pyridoxine replacement. The idiopathic or inherited forms of benign neonatal convulsions are also seen during this time period.

Components of a seizure

- Prodromal phase
- Aura
- Seizure (ictus)
- Post-ictal phase

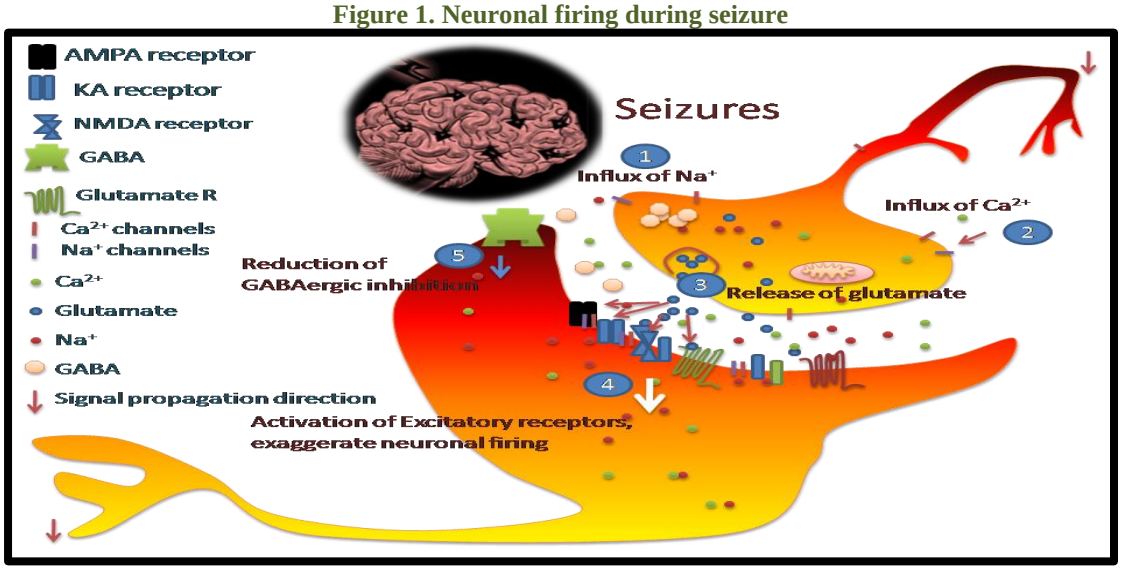
Characteristics of A Seizure

- The type of seizure
- The duration of the seizure
- The frequency of the seizures
- The time of day or night that the seizure occurs, and its relation to sleep
- The presence of an aura
- The presence of a post-ictal phase
- The age of onset

PATHOPHYSIOLOGY OF EPILEPSY:

A persistent increase of neuronal hyperactivity or excitation is a single characteristic in most of the epileptic syndrome. The anomalous behaviour of neurons is associated with causative factors which are mainly categorized into two groups: Chemical Imbalance and Brain Injuries. Chemical imbalance includes low blood level of sodium, calcium, sugar and oxygen. Brain injuries include intercranial haemorrhage, brain oxygen deficiency, infection, trauma, tumour, meningitis, stroke, and other neurological disorders. Other factors such as Genetic Factors and inflammation factors like Cytokines & tumour necrosis factor (TNF) are also involved. Neurological firing during seizure and pathophysiology of epilepsy are represented in Figure 1.

Figure 1. Neuronal firing during seizure



Neuronal firing is triggered by altered signal propagation. This may be the result of abnormalities in neuronal membrane stability or in the connections among neurons.

1. Epileptic bursts consist of sodium dependent action potentials
2. Calcium-dependent depolarizing potential. The opening of voltage activated Ca^{2+} channels and results in the flood of neurotransmitter (glutamate) into the synaptic cleft.
3. Increased the accumulation of glutamate activate N-methyl-D-aspartate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and
4. kainite receptors with consequent influx of Na^{+} and Ca^{2+} ions through the channels gated by these receptors leads to Neuronal hyper-excitability Uncontrolled increase in Disinhibition is also one of the key events in the generation of epileptic seizures.
5. Reduction of GABAergic inhibition is necessary to produce the synchronous burst discharges in groups of cells.

II. AIMS AND OBJECTIVES

Aims:

To evaluate monotherapy and combinational therapy and Quality of life (QOL) in epilepsy patients who are undergoing treatment with Anti-Epileptic drugs in Government Civil Hospital and Vijaya Neuro hospital, Karimnagar.

Objectives of the study:

General objectives:

To study and evaluate the effectiveness of monotherapy and combinational therapy of Anti-epileptic drugs in different age groups of patients and Quality of life of patients suffering from epilepsy.

Specific objectives:

- To identify the extent and use of monotherapy and combinational therapy of antiepileptic drugs in specific types of epilepsy in different age groups
- To know the effectiveness of combinational therapy in different types of epilepsy comparing to monotherapy
- To assess the different diagnostic criteria for epilepsy
- To assess pattern of EEG in different epilepsy patients
- To identify the accurate Risk factor causing epilepsy
- To assess the drug-drug interactions of other potential drugs interacting with Anti-epileptic drugs
- To assess the adverse drug reaction of anti-epileptic drugs
- To study the medication adherence behaviour
- To study therapeutic management of different types of epilepsy and broad spectrum antiepileptic drugs
- To determine the outcome of treatment of epilepsy in different age groups patients

III. METHODOLOGY

The study was conducted on Epileptic patients at Vijaya Neuro Hospital and Government Civil Hospital, Karimnagar which contain departments such as General Medicine, Cardiology, Neurology, Paediatrics, General Surgery, and Gynaecology and Auxiliary departments.

Study site:

Vijaya Neuro Hospital, Government Civil Hospital, Karimnagar.

Study design:

The study was prospective observational study.

Study duration:

The study was conducted over a period of six months (July2019-december2019).

Sample size:

300 Epilepsy patients.

Study criteria:

Inclusion criteria:

Patients diagnosed with epilepsy, including Co-morbid conditions associated with neuro and other General medicine conditions in both in-patients and out-patients department.

Categories included in the study are Children, Adults and Geriatrics of both the Genders between the age group of 1-80 years.

Patients associated with risk factors and complications of epilepsy.

Exclusion criteria:

Patients suffering from severe malignant syndromes were excluded.

Pregnant women's were excluded.

Sources of data:

- Patients who are suffering with symptoms of Epilepsy visiting the Vijaya Hospital and Government Civil Hospital for the diagnosis and treatment and also with past medical history of Epilepsy and co-morbid conditions.
- Interviewing and interacting with patients and patient care takers.
- Primary data through questionnaire which includes
- Name of the patient
- Age and gender
- Address
- Symptoms (Temporary confusion, Uncontrolled jerking movements of arms and legs, Loss of consciousness, Psychic symptoms (fear, anxiety, etc.)
- Diagnosis (Lipid panel, blood glucose & liver function tests, CT Scan, MRI ad EEG of brain)
- Electrolyte levels (Na^+, K^+, Ca^{+2}, Cl^-)
- Complications
- Duration of treatment.
- Patient data collection form (Annexure-a)
- Quality of life form (Annexure-b)
- Secondary data through internet, magazines, journals, text books, articles and etc.

Ethical Committee Approval:

The protocol of the study including the introduction, objectives, data collection form and methodology was submitted for approval of ethical committee members, the study was approved by Institutional Ethical Committee of Sree Chaitanya Institute of Pharmaceutical Sciences, Karimnagar.

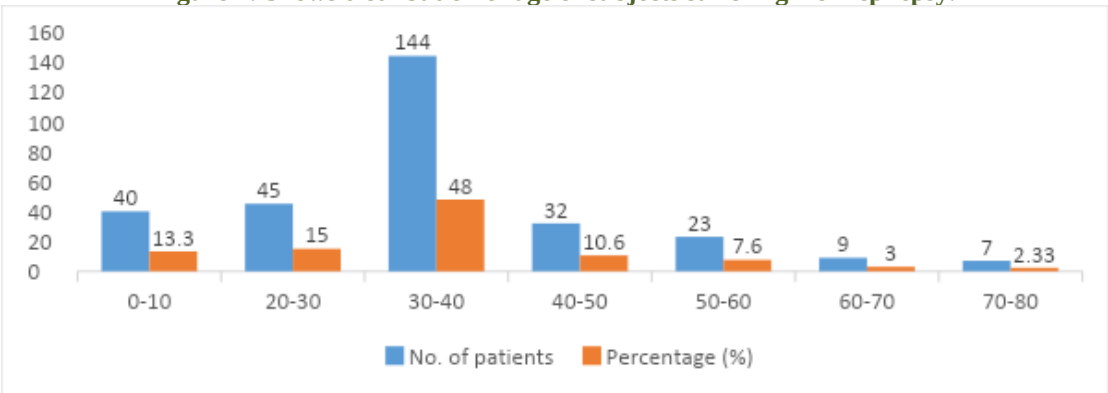
IV. RESULTS

A total of 300 subjects were considered for the study conducted on Evaluation of monotherapy and combinational therapy and QOL in Epilepsy including Co-morbid conditions. The data was collected from In-patient and out - patient department of Neurology.

Table No.1: Distribution of data according to age of epileptic patients

Age of Epileptic Subjects	No. of Patients	Percentage (%)
0-10	40	13.3
20-30	45	15
30-40	144	48
40-50	32	10.6
50-60	23	7.6
60-70	9	3
70-80	7	2.33

Figure 1: Shows distribution of age of subjects suffering from epilepsy.



In the above figure, it was observed that subjects suffering from epilepsy were highest in the age group 30-40yrs (n=144) having highest percentage of 48%, followed by (n=45) in age group of 20-30yrs with the percentage of 15, and in the remaining age groups the data was distributed from 0-10yrs i.e. 40 patients (13.3%), 40-50yrs i.e. 32 patients (10.6%), 50-60yrs i.e. 23 patients (7.6%) and the least was in age group of 60-70yrs i.e., 9 patients (3%) and 70-80yrs i.e., 7 patients (2.33%) respectively.

Table No.2: Distribution of data according to gender

Gender	No. of patients	Percentage (%)
Paediatric : Male	23	7.66
Female	10	3.33
Adult : Male	147	49
Female	80	26.66
Geriatric : Male	19	6.33
Female	21	7

Figure 2: Shows distribution of data according to gender

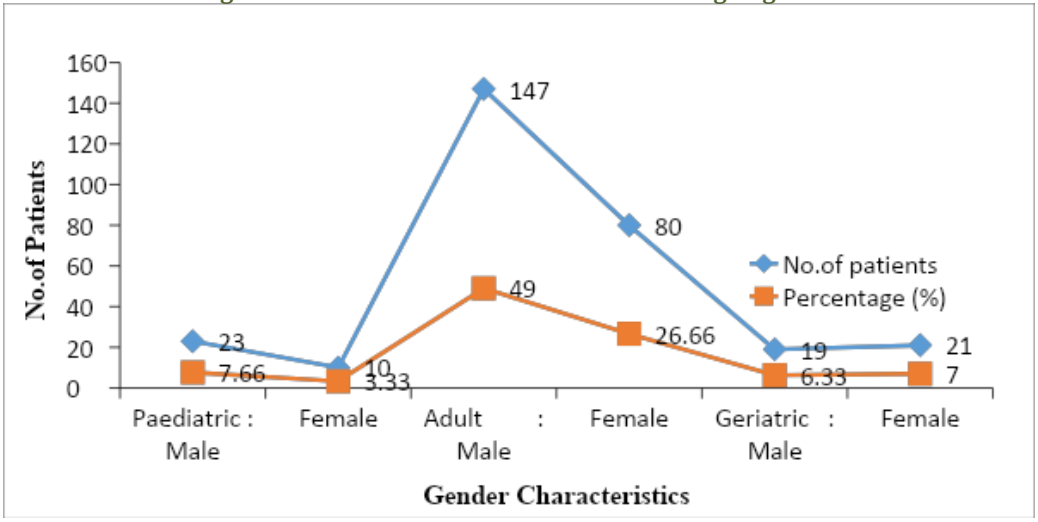


Table No.3: Distribution of data according to different types of epilepsy

Different forms of epilepsy	No. of patients	Percentage (%)
Status epilepticus	50	16.66
Focal seizures: ● complex partial ● simple partial	 12 7	 4 2.33
Generalized tonic clonic seizures	127	42.33
GTCS by alcohol dependence	46	15.33
Febrile seizures	33	11
Absence seizures	25	8.33

Figure 3: Shows distribution of different types of Epilepsy

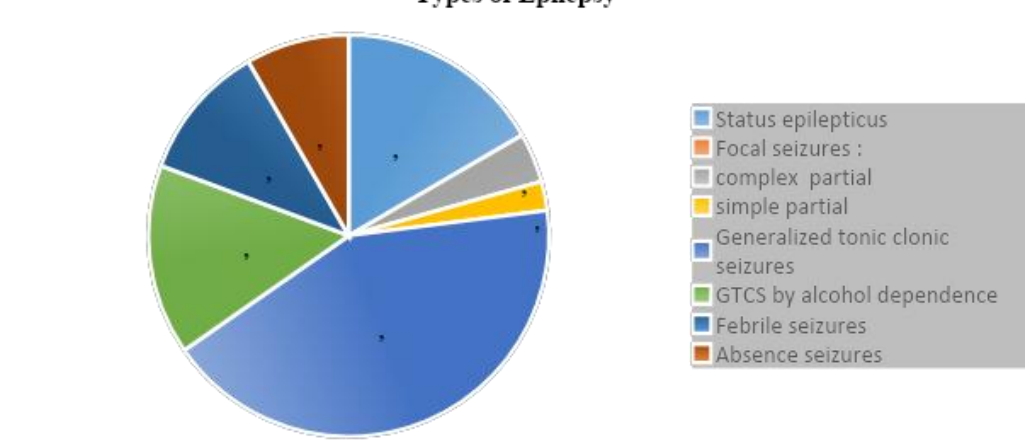


Table No.4: Distribution of data according to diagnosis

Diagnostic Parameters	No. of Patients	Percentage (%)
CBP	38	12.66
Biochemistry	23	7.66
X ray	12	4
EEG	85	28.33
ECG	12	4
CT SCAN	55	18.33
MRI	75	25

Figure 4: Shows distribution of data according to diagnosis

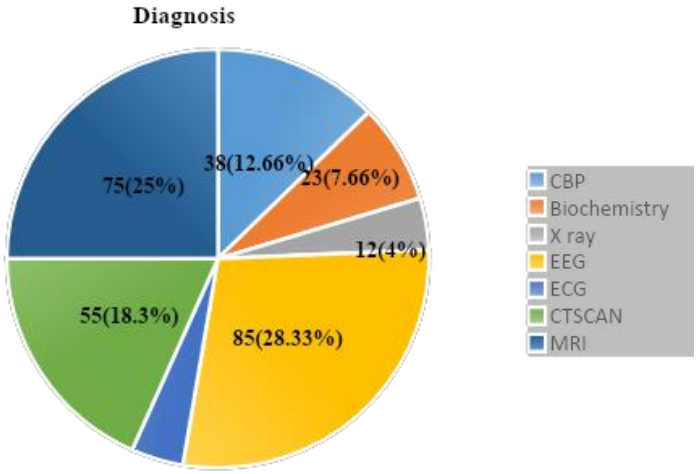


Table No.5: Shows distribution of data according to Monotherapy of Epilepsy

Indication	Monotherapy	No. of patients	Percentage (%)
GTCS (Generalizes Tonic-Clonic Seizures)	First line:		
	● Valproic acid	15	11.81
	● Lamotrigine	8	6.29
	● Topiramate	5	3.93
	Alternatives:		
	● Zonisamide	0	0
	● Phenytoin	12	9.44
	● Carbamazepine	3	2.36
	● Oxcarbamazepine	4	3.14
	● Phenobarbitone	2	1.57
	● Primidone	1	0.78
	● Felbamate	0	0

Focal Seizures	First line: ● Lamotrigine ● Carbamazepine ● Oxcarbamazepine ● Phenytoin ● Levetiracetam Alternatives: ● Topiramate ● Zonisamide ● Valproic acid ● Tiagabine ● Gabapentin ● Lacosamide ● Phenobarbital ● Primidone ● Felbamate	 3 2 2 1 1 1 1 1 1 1 0 0 0 1	 15.78 10.52 10.52 5.26 5.26 5.26 5.26 5.26 5.26 5.26 0 0 0 5.26
Absence Seizures	First line: ● Valproic acid ● Ethosuximide Alternatives: ● Lamotrigine ● Clonazepam	 2 13 1 0	 8 52 4 0
Status Epilepticus	First line: ● Lorazepam ● Diazepam ● Fosphenytoin ● Phenytoin sodium ● Phenobarbitone ● Midazolam Second line: ● Valproate ● Levetiracetam ● Lacosamide Third line: ● Pentobarbitone	 12 10 4 2 1 6 2 4 0 0	 24 20 8 4 2 12 4 8 0 0
Febrile Seizures	● Diazepam	12	36.36

The above table shows distribution of data according to monotherapy of epilepsy. Indication wise in GTCs which accounts for frequent diagnosis; Valproic acid was the 1st drug of choice as monotherapy in 27% of cases. In focal seizures Lamotrigine is used as first choice of drug. In absence seizures Ethosuximide is used as first line therapy. Whereas in status epilepticus and in febrile seizures lorazepam and diazepam is used as first line agent respectively. However add on therapy with another alternative antiepileptics is given in most of cases.

Table No. 6: Shows distribution of data according to Combinational therapy

Indication	Combinational therapy	No. of patients	Percentage (%)
Status Epilepticus	Phenytoin + Lorazepam	2	4
	Phenytoin + Lorazepam+ clobazam	1	2
	Phenytoin + phenobarbital	2	4
	Phenytoin + valproate	1	2
	Phenytoin + Levetiracetam + phenobarbital+ midazolam	1	2
	Phenytoin + levetiracetam +midazolam	1	2
	Phenytoin + Lorazepam + phenobarbital	1	2

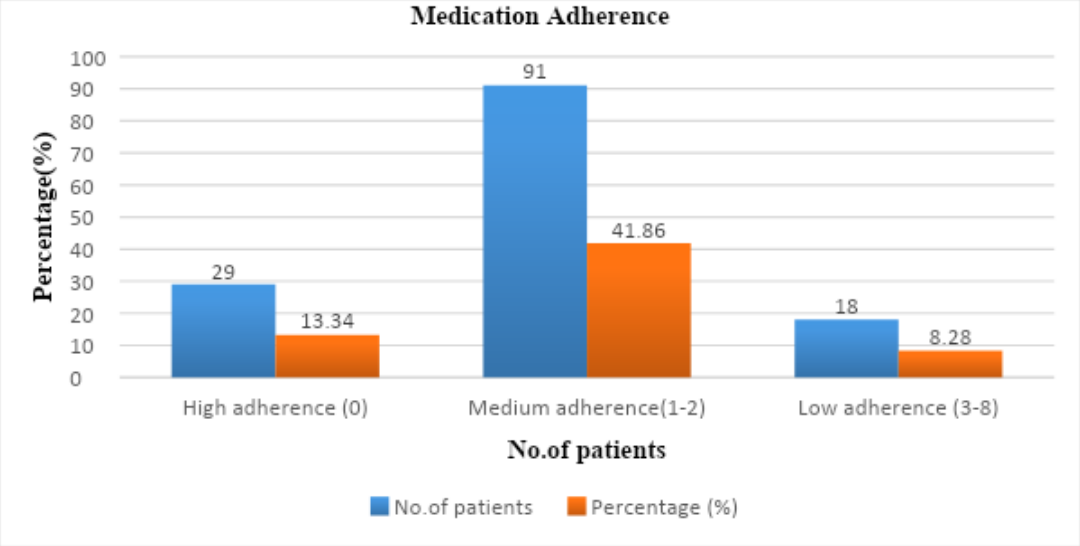
Focal Seizures: Partial Seizures	Phenytoin + clobazam	2	10.5
	Phenytoin + valproate	1	5.26
	Carbamazepine + Levetiracetam	1	5.26
Generalized Tonic Clonic Seizures	Phenytoin + Carbamazepine + Lorazepam	32	25.19
	Phenytoin + carbamazepine	8	6.29
	Phenytoin + carbamazepine + phenobarbital	4	3.14
	Phenytoin + phenobarbital	4	3.14
	Phenytoin + clobazam	3	2.36
	Phenytoin + lorazepam	5	3.93
	Phenytoin + Lorazepam + clobazam + Levetiracetam	4	3.14
	Phenytoin + carbamazepine + clobazam	1	0.78
	Phenytoin + clobazam + valproate	4	3.14
	Clobazam + Midazolam	12	9.44
GTC with Alcohol Abuse	Phenytoin + lorazepam	46	15.33
Febrile seizures	Carbamazepine + lorazepam	7	21.21
	Carbamazepine + Valproic acid	3	9.09
	Carbamazepine + clobazam	2	6.06
	Carbamazepine + phenobarbital	4	12.12
	Lorazepam + clobazam + Phenobarbital	3	9.09
	Lorazepam + phenobarbital	1	3.03
	Lorazepam + phenobarbital + Valproic acid	1	3.03
Absence seizures	Phenytoin + lorazepam + clobazam	3	12
	Phenytoin + carbamazepine	4	16
	Phenytoin + carbamazepine + clobazam	2	8

Above table shows distribution of data according to combinational therapy. In most of the cases of GTCS phenytoin plus lorazepam plus carbamazepine is used in 25% patients. Majorly in different types of epilepsy such as status epilepticus, focal partial seizures, Febrile and Absence seizures. Phenytoin is used with another antiepileptic drugs such as Carbamazepine, Clobazam and Lorazepam, Valproic acid, Levetiracetam and Phenobarbital.

Table No. 7: Medication Adherence Behaviour

Medication Adherence Level (Scale)	No.of patients	Percentage (%)
High adherence (3-8)	29	13.34
Medium adherence(1-2)	91	41.86
Low adherence (0)	18	8.28

Figure.7: Shows distribution of data according to Medication Adherence



Above figure shows that among 138 patients, majority of patients has shown medium type of adherence to AEDS i.e.91patients (41.86%), and high adherence (0) was observed in 29 patients (13.34%) are in baseline. Consequently 8.28% of patients were having low adherence (0) type of adherence.

V. DISCUSSION

The study provides insights on Evaluation of monotherapy and combinational therapy and QOL in Epilepsy.

In our study population of 300 patients; we analysed males (N=189, 63%) were predominant than females (N=111, 37%).A Study on trends in prescribing pattern of anti- epileptic drugs in tertiary care teaching hospital, by Murthy NV et al Murthy VN, Anusha B and Perumal P shows males were more frequently attacked with epilepsy than females [(11)] which complements our results. In contrast to our results the study conducted by T. Badwaik, Mahajan MH, Borker SA, Honrao R and Chopade SS on A drug utilization study of anti-epileptic drugs use in a tertiary care hospital of central India describes females were more effected than males in their study [(9)].

In a study conducted on Drug utilization pattern of anti-epileptic drugs: a pharmacoepidemiologic study. Journal of Clinical Pharmacy and Therapeutics by Hanssen Y, Dulue D, Al Balushi K, Al Hashar A and Al Zakwani I. and Caprio A et.al and Lim SH et.al shows from medicine units most patients were between 20-45 age groups [(10, 11, 12)] and our result is in accordance with it. In our study population of 300 subjects we frequently found the more adult i.e. (227) cases were reported with age group less than 45 years than paediatrics i.e. (33) cases.

In our hospital most patients were suffering from generalized tonic clonic seizures were accounted for approximately 42.33% followed by status epilepticus 16.66%, GTCS with alcohol 15.33%, febrile seizures 11%, Absence seizures (8.33%), focal seizures 6.33% .A study from Mysore, south India conducted by Sebastian J, Adepu R, Keshava BS and Harsha S. Assessment of antiepileptic drugs usage in south Indian tertiary care teaching hospital. Also shows approximately similar pattern of epilepsy [(7)].

The diagnosis of epilepsy is primarily based on careful clinical observation although EEG which is a valuable investigative tool. EEG abnormalities were recorded in 59.4% of epileptic patients in our study, which is comparable to 64.4% in study conducted by Ahmed MH, Obembe A. Electroencephalographic abnormalities in 351 patients with epilepsy [(13)] which is similar to our study conducted on 300 patients which reveals EEG abnormalities are present in 85 patients.

In GTCs which accounts for frequent diagnosis; Valproic acid was the 1st drug of choice as monotherapy in 20.45% of cases. However, add on therapy with another antiepileptics was introduced for 79.55% of cases along with other alternative drug. All the time phenytoin and another anti-epileptic drug were used in monotherapy of epilepsy.

Similar results were obtained by Sobhana et al. [(14)] except in one case where clobazam and midazolam which is given as inhaler was also used to treat GTC's. At maximum up to 4 different antiepileptic drugs were used to treat different indication. Ethosuximide is most frequently used in Absence seizures. In focal seizures Lamotrigine is used as first choice of drug.

Most commonly used add on antiepileptic was lorazepam followed by carbamazepine, phenobarbital, clobazam with phenytoin which is used as combinational therapy. Combinational therapy should be considered

when failure of two attempts of monotherapy [15] In our study up to 4 different antiepileptic drugs were prescribed in a prescription at maximum but combinational therapy by two antiepileptics were most common. These results are not in conjuncture with other studies. [8, 14, 16, 17] where they found that most of the patients (≥50%) were prescribed single drug. This may be due to the fact of failing of monotherapy or using Combinational therapy by physician at once in severe or life threatening situation. It is found that up to 60% of patients with epilepsy are noncompliant, and this is the most common reason for treatment failure [18].

Medication adherence Pattern of antiepileptic drug was studied in Epilepsy patient and it was observed that among 138 patients, majority of patients has shown medium type of adherence to AED's i.e.41.86%, which was supported by Archana Verma, Kiran K, and Alok Kumar. Medication Adherence to antiepileptic drugs in people with Epilepsy [20] and was opposed by Osterberg L and Blaschke T. Adherence to medication [19].

VI. CONCLUSION

The research was conducted on effectiveness of monotherapy and Combinational therapy in epilepsy patients and the data was collected, analysed and was concluded through the following conclusions. In our study it was concluded that, when compared to females; males were majorly affected with epilepsy and were in the age group of between 25 to 40 years. Different types of Epilepsies were considered in our study and treatment was given according to it and requires long term medication management. Initially monotherapy was the first choice for newly diagnosed epileptic patients. While monotherapy is preferred for initial treatment it may also fail for a variety of reasons LIKE it fails in patients who do not receive thorough evaluation and counselling by their physician, medication adherence, adverse drug reactions, compliance . Combination therapy is preferred when patient is unresponsive to monotherapy. Our study found that treatment with Valproic acid with Levetiracetam and also Carbamazepine with Phenytoin has shown better outcomes than other antiepileptic combinational drugs. We reported that a combination of Carbamazepine (CBZ) and Valproate (VPA) was more effective in different epileptic condition such as GTCs and Status epilepticus when compared with CBZ and VPA given as monotherapy.

It was also found that Valproic acid had better outcome and a combination of Levetiracetam with Valproic acid had superior outcome measured against other AED's, concluding the suggestions for the use of combinational therapy if initial monotherapy is unsuitable for the patients.

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