AN OBSERVATIONAL STUDY: TO ASSESS THE THERAPEUTIC OUTCOME AND PREVALENCE OF NEUROLOGICAL PSYCHOLOGICAL AND COGNITIVE EFFECTS IN PATIENTS TAKING ANTIEPILEPTIC MEDICATION

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INTRODUCTION

Epilepsy is defined as chronic non-communicable disease of brain affecting 50 million people worldwide. It can be distinguished by repeated seizures of an involuntary movement which involves partial body or entire body which sometimes is accompanied by loss of consciousness. The episodes of seizures are a result of excessive electrical discharges in the brain.[1]

70 million, people in the world have epilepsy marking the world's second most common neurological disorder.[2] With a conservative evidence, an estimate of 1% epilepsy of prevalence more than 12 million people are with epilepsy in India. At global level the prevalence of epilepsy is 5-9 per 1000 population. Most of male than female is said to be affected with epilepsy with overall a lesser difference. According to the Global Data, over 5 million are diagnosed by epilepsy each year.[2] The Comparison between High Income countries and Middle- and low-income countries shows us that epilepsy is more prevalent in middle- and low-income countries due to many endemic conditions and a higher incidence of road injuries, birth-related injuries which are not taken care at the earliest, poor health education and no optimal medical infrastructure.

The symptoms associated with epilepsy were fall into motor-- tingling, numbness, lip smacking, convulsive jerking incoordination, dystonic, chewing motions, Sensory - paresthesia, aura, auditory, gustatory, olfactory, visual, vestibular disturbances. Autonomic - sweating, flushing, pupil dilation, Behavioral -dysphasia, hallucinations, Cognitive-attention, memory impairment, forced thinking responsive impairment[3].There are two types of seizures- partial (seizure begins locally)-simple partial, complex partial and secondarily generalized seizures and generalized (bilaterally symmetrical and without local)-tonic- clonic, atonic, absence, myoclonic, status epilepticus[4].

Based on the Onset of Seizure Activity: Seizures are paroxysmal manifestations of cerebral cortex originates from grey matter of cortical and subcortical areas.[5] Seizures are alteration or disorientation, synchronous and rhythmic firing of population of brain neurons due to excessive firing there is sudden imbalance between excitatory and inhibitory neurotransmitters.[6] Initially small number of neurons fire abnormally that is locally results in partial seizures and if a greater number of neurons fire abnormally widely results as generalized seizures.[7]Based on Neurodevelopment: Neuronal Migration, Synapse Formation, Neuronal Connectivity, Extracellular Matrix. NEUROTRANMISSION: GABA, glutamate, dopamine, NA. Risk factors associated with epilepsy are mostly idiopathic origin, cryptogenic[8] and others- head injuries[9], trauma, vascular complications, infections, neurodegenerative disorders, tumors. Diagnosis of epilepsy involves physical examination, neurological tests[10,] EEG[11], MRI,[12] CT[13] scan, PET [14]and others which includes CBP, LFT, serum electrolytes.

As epilepsy is considered as third most common neurological disease, it requires treatment to control further episodes of attack for better quality of life. Antiepileptics are the primary pharmacotherapeutic agents considered effective in the treatment of symptoms and frequency of attacks associated with disorder. Based on type of seizure attack first line therapy includes older AED's carbamazepine, sodium valproate, phenytoin, clonazepam, diazepam, phenobarbitone as monotherapy[15]. Poor control of seizures required combination[16] or polytherapy[17]. But therapy on long term may be associated adverse effects and drug interactions[18] often led to use of newer

AED's[19] which have better efficacy[20], tolerability with fewer effects - levetiracetam, valproate, clobazam, lacosamide. Non pharmacological treatment consists of surgeries- vagal nerve stimulation, deep brain stimulation and ketogenic diet.[21,22,23,24] The efficacy was based on medication adherence and adverse effects associate with AED's are sedation, jerks, tremors, ataxia, visual disturbances, cognitive effects- memory and attention impairment, difficulty in concentrating, fluency in language, behavioral disturbances, anxiety, hallucinations.[25]

- The main objective of the study is to find out the therapeutic outcome of subjects taking Anti-Epileptic medications by Epilepsy Project questionnaire, and to know the prevalence of neurological, psychological and cognitive effects of subjects on AEDs by BPRS scale and Addenbrooke's Cognitive Examination scale

MATERIALS AND METHODS

A prospective observational study was conducted at neurology outpatient department (OPD) in, a tertiary care hospital for a period of 6 months (January 2021 to June 2021).

The data was collected from OPD and IPD by interviewing the patients or care providers. The data collection format was verified and authenticated by the hospital preceptors for the study. Study involved 215 subjects who were diagnosed with epilepsy. Patients below 7yrs, pregnancy cases, mental retardants, Drug dependence and substance abuse cases were excluded from study.

Written informed consent form was taken from patient or care provider to collect data. The data form includes Socio-demographic information like age, gender, marital status, past medical history, past medication history, social history, history of epilepsy, types of seizures and also Epilepsy project questionnaire, Adden Brooke's cognitive examination scale

(ACE-III), Brief psychiatric rating scale (BPRS) were attached to it.

Statistical Analysis: Descriptive statistics was done by using SPSS software to determine mean and standard deviation of collected data. The statistical tool Chi square test was performed to determine P-value between the different variable with data collected (History v/s Frequency, Type's v/s Quality of Life, History v/s Neurological Effects, History v/s Cognitive Effects, History v/s Psychological Effects, Cognitive Effects v/s Drugs, Psychological Effects v/s Drugs). The P-value is used in determining the statistical significance within statistical hypothesis for drug related effects in epileptic patients to base line visit. The P-value was set at <0.05 and confidence interval was 95%.

RESULTS

In present study around 215 cases were included as per our criteria. **Table -1** indicates socio demographic background which includes standard deviation and P- value of various parameters considered in our study. There were female patients (60%) predominant over male's (40%). 21-30 yrs. (20.9%) patients are the most effected than the other age groups, married (79%), history of seizure attack one month (23%), number of patients with past medical history (81%).The (42%) LOC, (40%) jerking movements,(40%)of up rolling of eyes(35%) headache are most commonly associated symptoms in epileptic patients and in case of types of seizures, GTCS(32%)were predominant over other type of seizures as followed-simple partial(23%), complex partial (20%) localized related epilepsy-LRE(19%)and status epilepticus SE(7%) as mentioned in **Figure -1.** The p value was found to be clinically significant (P-value < 0.05) for the entire variables at confidence interval 95%.
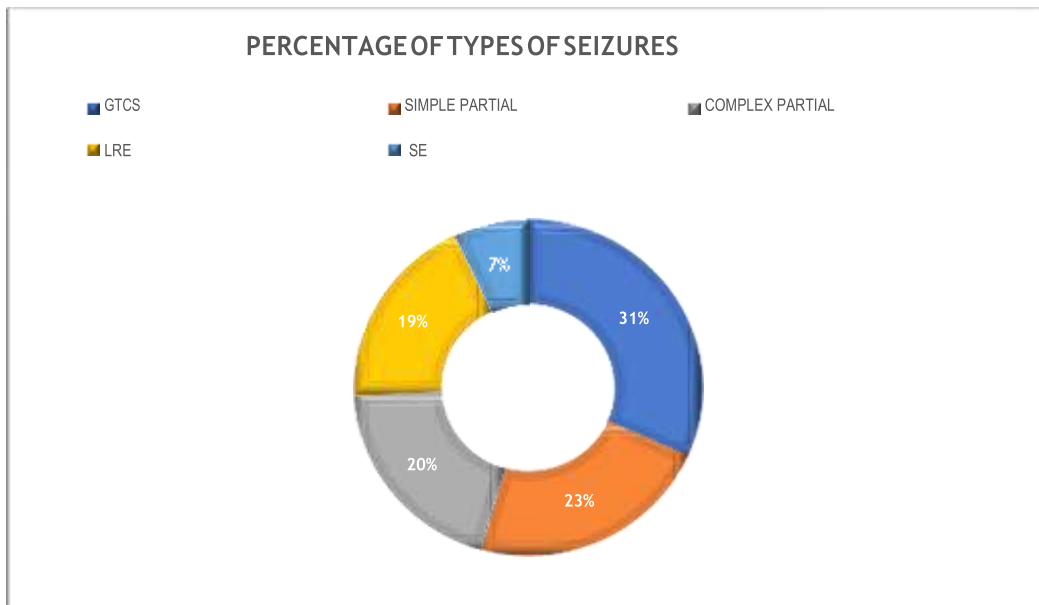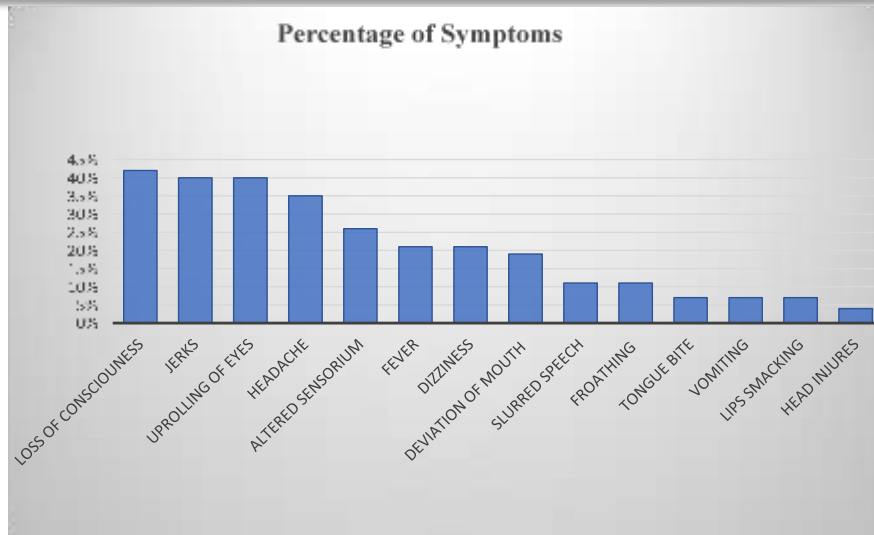
Figure-1: Represents The Percentage Of Symptoms And Types Of Epilepsy.

Table-1: Socio-Demographic Details.

Category	Sub category	Number of Patients:	Standard Deviation:	P-value:
Age	11-20yrs	25		
	21-30yrs	45		
	31-40yrs	35		
	41-50yrs	35	17.915	0.0052
	51-60yrs	25		
	61-70yrs	35		
	71-80yrs	15		
Gender	Males	85	0.491	0.0073
	Females	130		
Marital status	Married	170	0.420	0.0038
	Unmarried	45		
History of epilepsy	One week	50		
	>one month	50		
	3 months	25		
	6months	20	2.108	0.0024
	One year	20		
	3years	30		
	>5years	20		
Types of epilepsy	GTCS	70		
	Simple partial	50		
	Complex partial	45	1.253	0.0083
	LRE	40		
	Status epilepticus	10		
Medication adherence	Adherent	126	0.462	0.0071
	Non adherent	89		
Neurological effects	Nausea	26		
	Headache	34		
	Sedation	53	1.686	0.0024
	Tingling	12		
	Numbness	152		
	dizziness	63		
Cognitive effects	ACE-III SCORE	215	0.822	0.0051
Psychological effects	Psychological BPRS	215	1.302	0.0079

As per prescription pattern monotherapy (17%) and polytherapy (37%) was less preferred than combination therapy (46%) and number of patients on monotherapy (37), combination (132) and polytherapy (46) as mentioned in **Table-2, Figure -2**, and newer antiepileptics are the most prescribed drugs. When it comes percentage of drug used levetiracetam (80%) is most prescribed and carbamazepine (5%) is the least were also as seen in **Figure-2.** Both medication adherence was more in females (58.3%) than males (38.5%) and quality of life was good among (38.5%),pretty good in(30.8%)very good(23.1%)and pretty bad(7.6%) were shown in **Figure-3** and present health status of epileptic patients was being analysed by using Epilepsy Project Questionnaire as shown in **Table -2** and therapy related neurological effects-(44%) associated with numbness and least effect reported(4%)tingling was shown in **Table-3**,represents the percentage of neurological effects recorded **Figure -4**.The cognitive effects was more prevalent in males - memory(26%),fluency(21%),language(14%),visuospatial(12%)andattentionwaslessnoticed(23%)than females was shown in

Table-3and **Figure-4** represents the cognitive effects using Adden Brookes Cognitive Examination Score and psychological effects was recorded using Brief Psychiatry Rating Scale which categorised into- mild ,very mild and moderate effects are in **Table-3,Figure-4-**represents the psychological effects includes- **very mildly**

recordedhallucinations(84.6%)werehigh,behaviouralchanges(69.3%)depression(37.5%),anxiety(33.3%)moodchanges(30.8%)were least, and in **mild** -mood changes(46.2%) are high and hallucinations(15.4%) was least , In **moderate-**mood changes(30.8%) were high and behavioural changes (23.1%) were less in epileptic patients Chi square test was performed between variables (History v/s Frequency (0.008), Type's v/s Quality of Life (0.0073), History v/s Neurological Effects (0.009), History v/s Cognitive Effects (0.007), History v/s Psychological Effects (0.0063), Neurological Vs Drugs (0.0079), Cognitive Effects v/s Drugs (0.008), Psychological Effects v/s Drugs (0.007).and P-value was clinically significant (<0.05).

TABLE -2: Represents the prescription patterns and present health status of epileptic subjects.

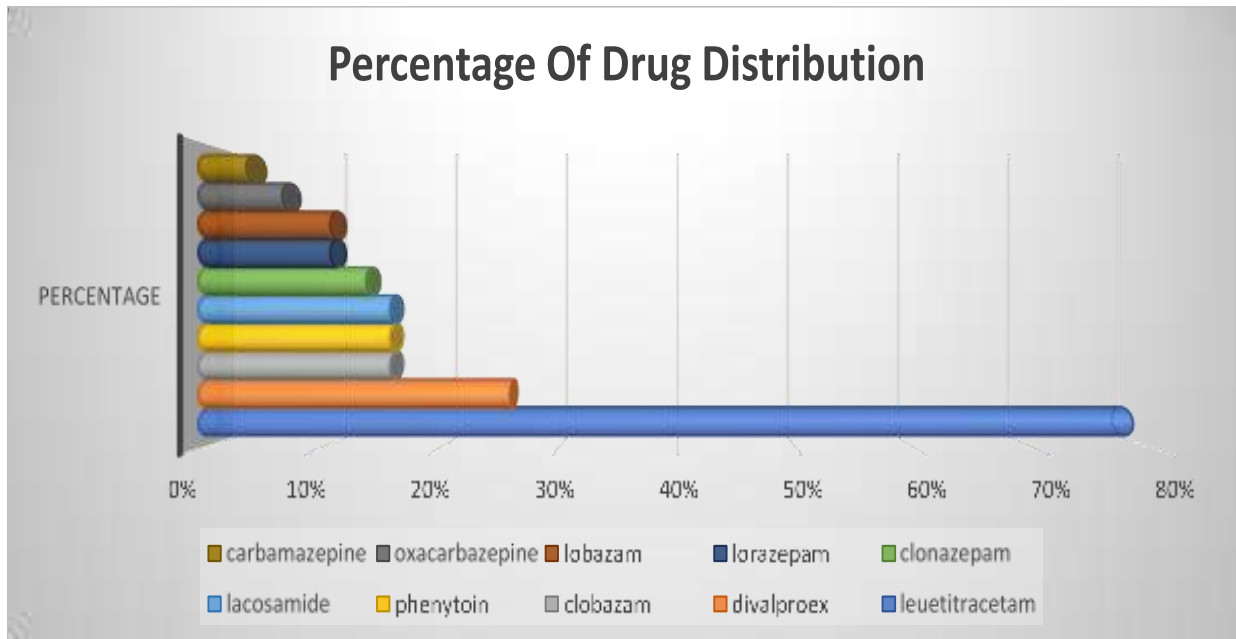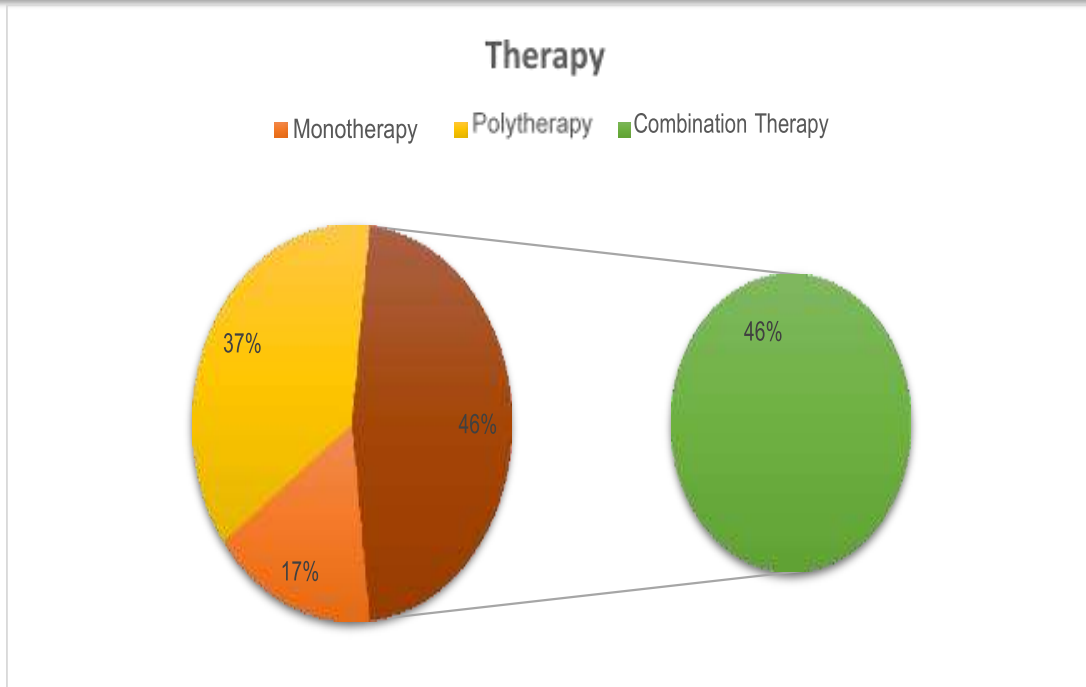| 1. Prescription patterns of Antiepileptics:			
Types of therapy	**Monotherapy**	**Combination therapy**	**Polytherapy**
No. of patients	37	132	46
2. Present health status of epileptic patients:			
Category	**I have no problem**	**I have problem**	**I am unable to perform**
Mobility	184 Pt	24Pt	9Pt
Self- care	174Pt	25Pt	16Pt
Usual activities	174Pt	33Pt	8Pt
Pain/discomfort	165Pt	41Pt	8Pt

Figure -2: Representation of Percentage of Types of Therapy and Percentage of Drug Distribution
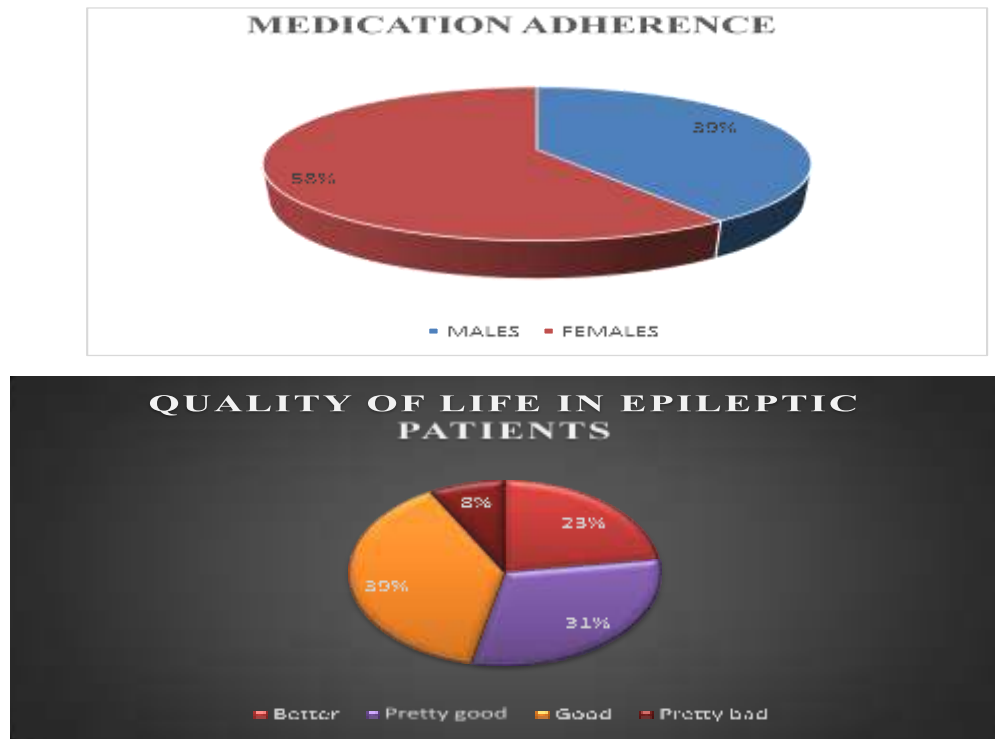
Figure-3: Represents the Medication Adherence and QOL in Epileptic Patients

TABLE-3: Represents the neurological,cognitive, psychological effects of antiepileptic drugs

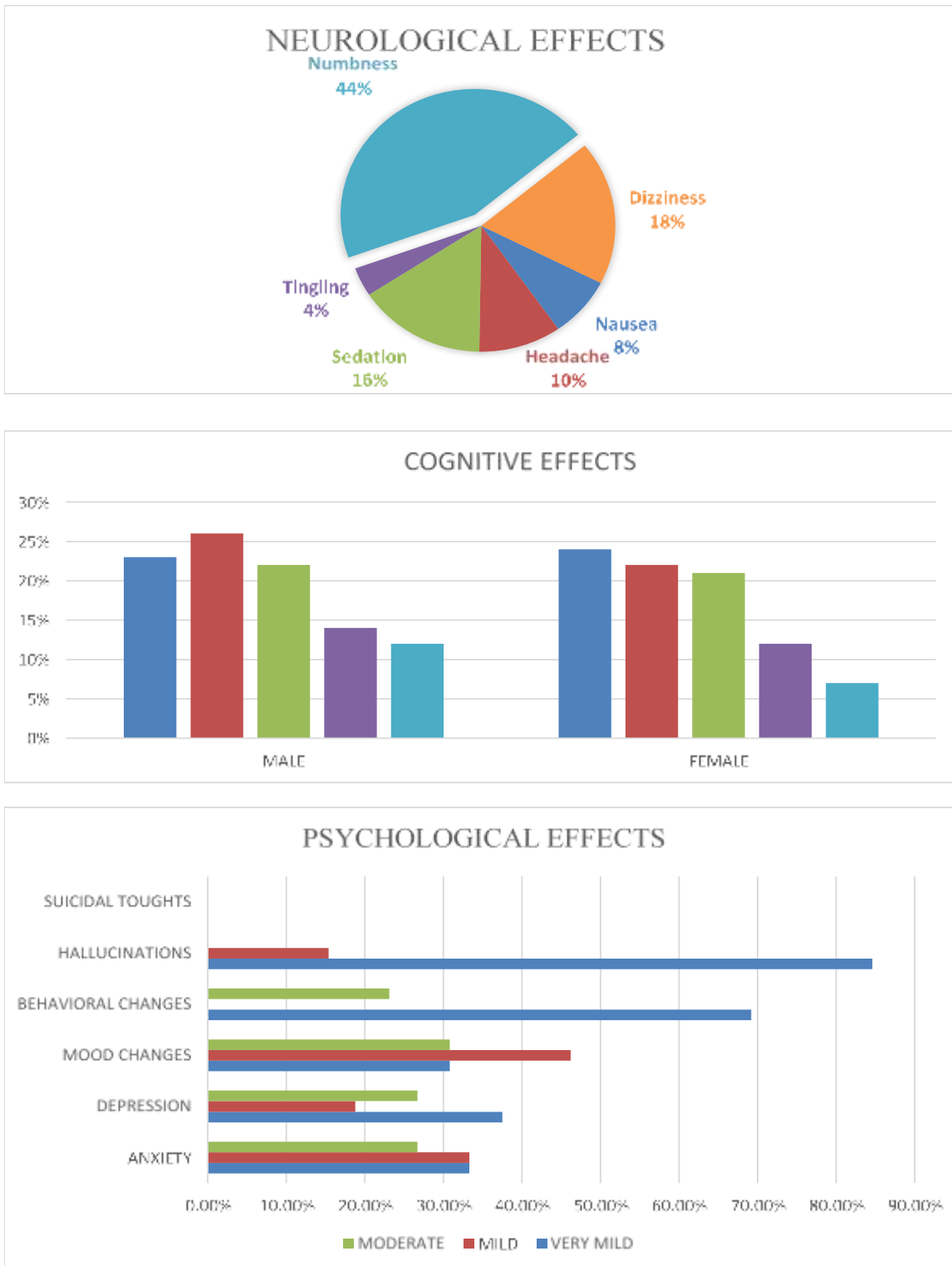| Neurological effects of antiepileptic drugs:						
EFFECTS	**Nausea**	**Headache**	**Sedation**	**Tingling**	**Numbness**	**Dizziness**
MALE	10	17	35	8	75	43
FEMALE	16	17	18	4	77	20
TOTAL	26	34	53	12	152	63
Percentage of cognitive effects of antiepileptic drugs using ACE-III SCORE:						
EFFECTS	**Attention**		**Memory**	**Fluency**	**language**	**Visuospatial**
MALE	23%		26%	22%	14%	12%
FEMALE	24%		22%	21%	12%	7%
Percentage of psychological effects of antiepileptic drugs using BPRS scale:						
EFFECTS	**Anxiety**	**Depression**	**Mood changes**	**Behavioural changes**	**hallucinations**	**Suicidal thoughts**
VERY MILD	33.3%	37.5%	30.8%	69.2	84.6	-
MILD	33.3%	18.8%	46.2	-	15.4	-
MODERATE	26.7%	26.7%	30.8	23.1	-	-

Fig-4: Represents the neurological, cognitive and psychological effects of epileptic patients

DISCUSSION

"AN OBSERVATIONAL STUDY: TO ASSESS THE THERAPEUTIC OUTCOME AND PREVALENCE OF NEUROLOGICAL, PSYCHOLOGICAL AND COGNITIVE EFFECTS IN PATIENTS TAKING ANTIEPILEPTIC MEDICATION'', was conducted in a tertiary care hospital considering both out-patients and in-patients. The data was collected for 215 patients using data collection forms.

In our study, among 215 patients, 40% were males and 60% were females. Our study has relatively high number of patients (20.9%), of age group between 21-30 years. Whereas the age groups 31-40, 41-50 and 61-70, also hold a pretty high number of patients (16.27% each). In our study, 79% of the patients were married and the remaining 21% were unmarried. The patients were with various past medical history. Out of which, Hypertension, Diabetes mellitus and hypothyroidism stands high in the row. Hypertension was seen in 60 patients, in which females were 45. Type-2 Diabetes mellitus was seen in 35 patients (15 males& 20 females). 25 female patients with hypothyroidism were reported. There were also other different types of past medical history like CVA, CKD, neuropathy, encephalopathy, dementia, drop attacks, TIA, CSVT reported in patients, but in less numbers. 145 patients were diagnosed with epilepsy in last 6 months and 70 patients have seizures history from past 1 to 2 years. In our study, the social history of patients was considered. In males, 50 patients have smoking, 125 have alcohol and 25 patients have both habits. This number is significantly low in females, 10 patients have alcohol habit and 5 have both smoking and alcohol habits. In the patients diagnosed with epilepsy in our study, generalized tonic clonic seizures were the most commonly seen, accounting 30% of total. Simple partial and complex partial seizures have equal share in diagnosis, i.e., 21% each. Focal seizures were seen in 14% and Localized Repetitive Epilepsy in 10%. Status epilepticus was least diagnosed in the study (2%). Checking with symptoms, major presenting complaints were loss of consciousness (42%), jerking movements (40%), up rolling of eyes (40%), altered sensorium (26%), dizziness (20%) and deviation of mouth (19%). The less common symptoms were, slurred speech (11%), frothing (11%), tongue bite (7%), vomiting (7%), lips smacking (7%) and head injury (4%). The study was majorly focused on antiepileptic medication. Where we have studied their efficacy and prevalent neurological, psychological and cognitive effects. Levetiracetam was the most prescribed drug for the patients, might be in monotherapy, combination or polytherapy. It is prescribed more in combination therapy (in 70 patients). Totally 185 patients were given this drug. Next stands the drugs Divalproex (in 55 patients), locasamide (in 40 patients), clobazam (in 35 patients), phenytoin (in 35 patients), lobazam (in 30 patients), lorazepam (in 20 patients), clonazepam (in 15 patients), carbamazepine (in 10 patients), and Oxcarbazepine (in 5 patients). These drugs were given either in monotherapy or in combination or polytherapy. In our study, combination therapy was the most prescribed, accounts for 46% of patients. In 37%

of the patients polytherapy was prescribed and the monotherapy in 17% of patients. Medication adherence was assessed in all the patients. Out of 215 patients, 208 patients were adherent to their medication, in which males were 83 and females were 125. Medication adherence in patients with epilepsy by Salvaggio suggest that it is important to improve the medication adherence in patients with epilepsy, because if taken properly, anti-epileptic drugs can reduce the frequency of seizure attack, thereby improving the quality of life and reducing the number of hospitalizations and emergency room visits[26] .

Using three scales namely EPILEPSY PROJECT QUESTIONNAIRE, ADDENBROOKE'S COGNITIVE EXAMINATION and BRIEF PSYCHIATRIC RATING SCALE, the health status, quality of life and various effects were assessed in patients. In present health status, factors like mobility, self-care, usual activities and pain/discomfort were checked. 184 patients have no problem in mobility, while 24 patients have problem and 9 patients were unable to perform. 174 patients have no problem in self-care, while,25 patients have problem and 16 patients were unable to perform. Coming to usual activities, 174 patients have no problem, 33 patients have problem and 8 patients were unable to perform. 165 patients have no pain/discomfort, 41 patients have pain/ discomfort and 8 patients suffer more from this. Therapeutic outcome was measured using Epilepsy project questionnaire, where past four weeks seizure history was taken. Among 215 patients, 10 patients have one episode of seizures, 06 patients have two, 07 patients have three episodes, 03 patients have four episodes, 02 patients have five episodes and 07 patients have six& more episodes of seizures. Coming type of seizures, 8.83% patients had Major type of seizures 7.44% patients had Mild seizures and 83.7% patients didn't experience a seizure in past 4 weeks. We can assess the outcome of therapy based on the control of seizures, which is the main goal of treatment. Antiepileptic drug treatment: outcomes and adherence by W R Garnett shows New antiepileptic drugs (AED) increase the likelihood of effective treatment for patients who have failed initial treatment. Through cooperation, patients and clinicians can maximize the effectiveness of AED treatment and the potential to achieve the desired goals and results. The choice-based drug selection will help achieving goals of therapy[27] . When asked for quality of life, 50 patients rated very good, 66 patients said pretty good, 83 patients have good and bad mix, 16 patients experienced pretty bad quality of life. No patient has very bad quality of life. Quality of Life in Patients with Epilepsy and Impact of Treatments by Patrizia Berto suggest that the frequency of seizures seems to be one of the most relevant determinants of poor quality of life (QOL) scores, and quality of life is worsened by the coexistence of depression. There are no detailed or even conflicting results regarding the effects of medications. Role activity, emotional state and cognition have always been the most studied areas of quality of life in epilepsy research[28] . Among 215 patients, the Cognitive Effects were analysed using "Addenbrooke's cognitive examination scale".

23% of male patients and 24% female patients suffered from attention deficit. The patients were assessed for memory disturbances, found that 26% males and 22% females suffered from memory disturbances. 22% males and 21% females have problem with fluency. With ACE scale, language of the patient was also assessed, which found 14% males and 12% females have problem in language. Visuospatial abilities were decreased in 12% males and 7% females. A study named Effect of Antiepileptic Drugs on Cognitive Function in Individuals with Epilepsy by Lars Brunbech, Anne Sabers says changes in cognition may reflect the chronic side effects of AED, but the negative effects of drugs are only one of several factors that may affect cognition. In addition, subjective complaints about cognitive deficits (such as memory problems or attention) may also reflect other aspects of adverse reactions, rather than those involving specific cognitive functions (such as mood and anxiety) [29]. Prevalence of cognitive effects was seen in patients (who were included in our study) taking AEDs. Based on subjective evidence, the neurological effects were noted. 44% of the total patients complained numbness, 18% patients experienced dizziness, sedation was seen in 16% patients, also headache (10%), nausea (8%) and tingling sensation in 4% patients. In our study, we used "Brief psychiatric rating scale", to assess the psychological effects. There were no severe psychological conditions observed. But very mild to moderate psychological effects were seen in patients. Anxiety was very mild in 71 patients, mild in 71 patients, and moderate in 57 patients. Very mild depression was seen in 80 patients, mild depression in 40 patients and 57 patients have moderate type of depression. 66 patients experienced very mild mood changes, while 99 patients experienced mild and 66 patients experienced moderate changes in mood. Behavioural changes were observed in 150 patients and moderate change of behaviour in 49 patients. Hallucinations were also seen during assessment. 182 patients have very mild hallucinations and 33 patients have mild hallucinations. A small number of patients with epilepsy are aggressive. An Evidence-Based Review of Antiepileptic Drugs, and Aggression by Martin J. Brodie, Frank Besag et. Al suggests that it is rarely associated with seizures, but it occurs between seizures, sometimes as part of complex mental and behavioural comorbidities, and sometimes related to AED treatment[30]. Here in our study the behavioural effects prevailed, but in minor scale.

CONCLUSION

Epilepsy is a chronic disease that can cause unprovoked, recurring seizures. A seizure is a sudden electrical activity in the brain. There are two main types of seizures- Generalized seizures affects the entire brain, focal or partial seizures affect only part of the brain. There are 50 million people with epilepsy in the world, most of whom live in developing countries. There are about 10 million people with epilepsy in India. Antiepileptic drugs when used regularly have good therapeutic outcome. Adherence is directly proportional to the therapeutic outcome. More the adherence, more will be the outcome. Selection of drug will be a choice, for better efficacy. Newly diagnosed patients will be generally given monotherapy or combination of AEDs to treat Epilepsy. Polytherapy will be initiated on need based. The study found that polytherapy or combination will have good therapeutic outcome. In few newly diagnosed patients' monotherapies also worked better. Most patients received the new AEDs. Combination of classic and new AEDs are more commonly used in patients with epilepsy & related comorbidities. Efficacy was in satisfiability range (83.7%) when assessed with scale (Epilepsy project questionnaire), in our study. Thus, range of therapies depending on patient condition showed better control of seizures. Since drug-based epilepsy treatments are mostly long-term, sometimes lifelong-treatment, it is particularly important to consider adverse interference effects. In addition to the frequency of seizures, cognitive and psychological side effects are particularly serious for patients' quality of life. The study found that there was prevalence of neurological, psychological and cognitive effects. The neurological complaints were recorded during our study. The psychological effects were assessed with BPRS scale, which found patients have different type of psychological conditions. The study also found the cognitive effects which was assessed by ACE scale. Cognitive impairment, from very mild to moderate was seen in patients, on treatment. Our study concluded that the treatment with newer AEDs, a combination of newer and classical AEDs showed better efficacy. This study also found that patients who were on medication from long duration have experienced psychological and cognitive problems. Neurological effects were observed in newly diagnosed patients who were taking AEDs. Better and safer drug selection will lead to better efficacy and fewer side effects. Newer AEDs will be a better choice over classical AED.

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