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ASSESSMENT OF PRESCRIBING PATTERN, COMPLIANCE AND ADVERSE DRUG REACTIONS WITH ANTIEPILEPTIC PHARMACOTHERAPY

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ABSTRACT

Approximately 50 million people worldwide have epilepsy, making it one of the common neurological diseases globally. People with epilepsy require prolonged treatment and monitoring. The main goal in the treatment of epilepsy should be adequate control of seizures, without causing any life threatening reactions due to medications. The objective of study was to assess the pattern of prescribing, compliance and adverse reactions with antiepileptic drugs used in different types of epilepsy. A prospective observational analysis of epilepsy cases admitted to KR Hospital over a period of 6month from November 2018 to April 2019 was carried out with a sample size of 120. Patient's demographic data were collected by using patient's data collection form. And ADRs were assessed by using Naranjo causality assessment scale and Hartwig severity scal The data obtained was analyzed by using SPSS version 20. In our result majority of the patients were female and age group was 31-45 year. Generalized tonic-clonic seizure (43.3%) was the major type of epilepsy (n=52). Phenytoin was the commonest drug prescribed for its treatment (77.5%) followed by levitriacetam. Common adverse effect associated with antiepileptic drugs were skin rashes, headache, gum bleeding and thrombocytopenia. Skin rashes was the most commonly reported ADR (n=7). We found that phenytoin was the antiepileptic drugs causing most number of severe ADRs. 43.24% ADRs were mild, 54.05% were moderate and 2.7% were severe. 37.83% ADRs were probable, 59.46% were possible and 2.7% were definite category. According to the study4 49.2%% were compliant to the medication while 50.8% were incompliant. 63.3% of the patients stated education as the reason for non- compliance. GTCS was the most commonest type of epilepsy recorded. Our study reveals that the conventional AEDs are commonly used. Poly-therapy was the most preferred therapy pattern for epileptic patients, this indicates that the epileptic patients should be closely monitored for ADRs, to avoid clinically significant harmful consequences. Most of the patients are drug compliant.

KEYWORDS: Epilepsy, Antiepileptic drugs (AEDs), Prescribing pattern, Adverse drug reactions (ADRs), compliance.

INTRODUCTION

Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures. A seizure occurs when there is a sudden and brief excess urge of electrical activity in the brain between nerve cells. This results in an alteration in sensation, behavior, consciousness.1 There are many kinds of seizures, each with characteristic behavioral changes and Electro physiological disturbances that can usually be detected in scalp Electro encephalographic (EEG) recordings. A seizure is a transient epileptic event, indicating a disturbance in brain function.2 Approximately 50 million people worldwide have epilepsy, making it one of the common neurological diseases globally. Epilepsy is a challenging medical problem in India with an annual incidence of 27.27 per 1,00,000 population and prevalence of 572.8 per 1,00,000.3 People with epilepsy require prolonged treatment and monitoring. There are currently more than 25 drugs in the market for the treatment of epilepsy. The main goal in the treatment of epilepsy should be adequate control of seizures, without causing any life threatening reactions due to medication. Antiepileptic drugs are increasingly being prescribe to patients of all ages in populations worldwide either as monotherapy or polytherapy. The prescribing of first - choice AEDs, in particular, has changed over the last decade, with prescribers tending to prescribe newer AEDs to patients due to their improved tolerability. So studies about prescribing pattern of AEDs are essential.4

Epilepsy is a chronic condition often requires long term treatment. Due to the long duration of treatment, various adverse reactions are seen (Eg: sedation, tremor, coordination disturbances, dizziness etc…). Adverse

drug reactions are one of the drug related problems being considered as the important cause of hospital related admissions and are a challenge for drug safety. ADR not only account for significant morbidity mortality but can also lead to increase in the length of hospital stay and health care cost. So identifying and reporting of ADRs of antiepileptic drugs are essential.5 Epilepsy may promote limitations and restrain activities, interfering with the occupational ability, professional goals and social integration of patients. It increases morbidity and symptomatic epilepsy reduces life expectancy by 18 years at maximum. It continues to be a highly stigmatized and disabling chronic condition requiring a lifelong process of adherence to the prescriber's instructions and drug regimens. But many people cannot follow the order and seizure can occur from antiepileptic withdrawal. So measuring and monitoring of drug compliance is essential.6 The purpose of our study is to investigate the changes in prescribing pattern of antiepileptics, exposure of specific drugs to certain patient groups, combination of drugs, and possible adverse reactions with antiepileptic drugs.

MATERIALS AND METHODOLOGY

A prospective observational study conducted at Mysore medical college and research institute, Mysuru. The study was carried out in patients of Neurology department, patients with epilepsy. The study duration was 6 months, from November 1st 2018 – April 30th 2019.

Ethical approval was obtained from the institutional ethical committee of Mysore medical college and research institute and associated hospital, Mysuru.

Subject of both sex and age above 18 years were included into the study over the period. The patients who were referred to the higher centres were excluded from the study. The data were collected from the case record of patients and their bystanders respectively after getting informed consent. A specially designed data collection form was devised for the study. All relevant data of the enrolled patients including demographic details; clinical data such as diagnosis, type of epilepsy, laboratory data, past medical history, past medication history, comorbidities; therapeutic data such as drug name, dose, frequency, route and duration of administration was collected from various data sources. Adverse drug reaction (ADR) datawere captured on the ADR monitoring form of Pharmacovigilance programme of India. Causality assessment was done on the basis of Naranjo scale criteria.

After collection, all data were checked thoroughly for completeness and errors. All enrolled patients were reviewed on the basis of treatment to identify patient drug compliance. Results were analyzed based on the study objectives using suitable statistical methods. Statistical package for social science (SPSS) was used to analyse the data. The data's were expressed as mean +/- standard deviation, frequency and percentage. ANOVA (p), Chi Square, confidential interval (CI) and odds ratio were used to identify significance.

RESULTS

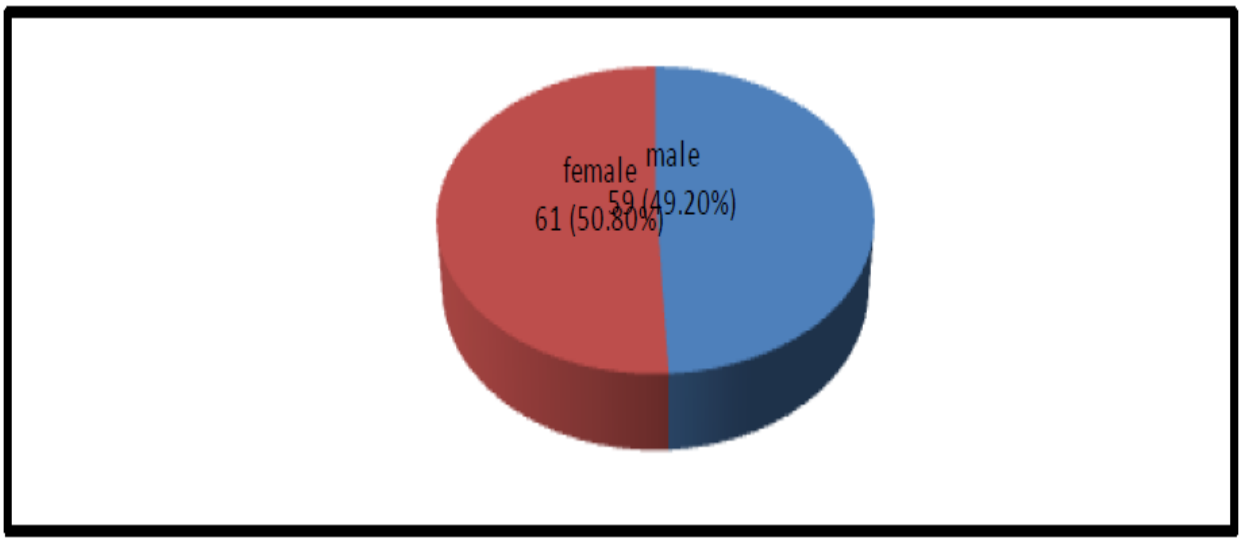

Figure 1: Gender distribution in the study population.

Table 1: Age categorization in the study population.

Gender	Patient age group(years)	Number of patients (n=120)	Percentage
Male	18-30	9	7.5
	31-45	18	15
	46-60	10	8.3
	61-75	17	14.1
	>75	5	4.2
Female	18-30	13	10.8
	31-45	19	15.8
	46-60	14	11.6
	61-75	13	10.8
	>75	2	1.6
Total	18-30	22	18.3
	31-45	27	22.5
	46-60	24	24
	61-75	30	25
	>75	7	5.8

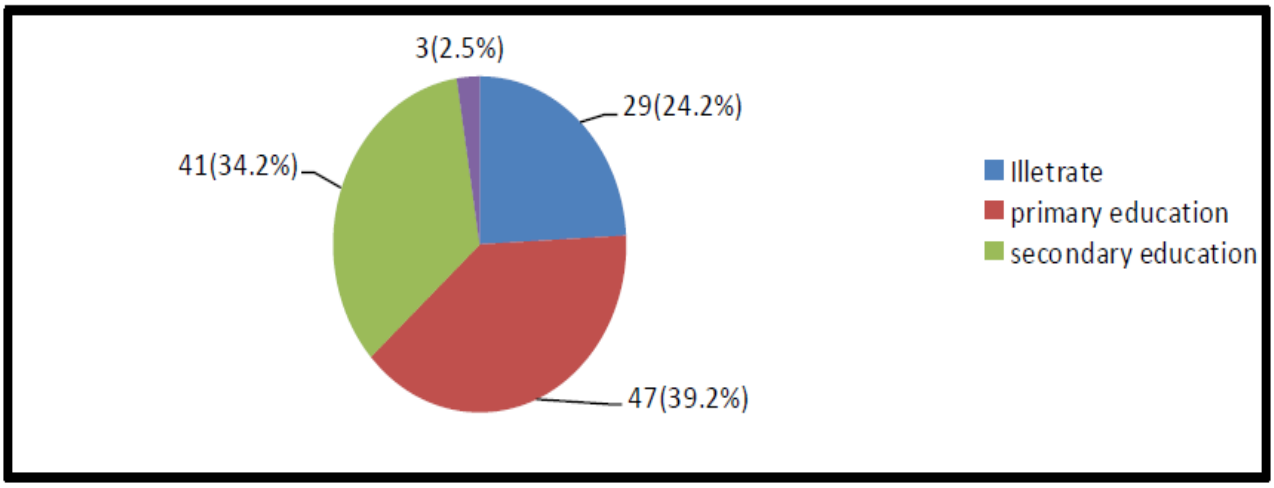

Figure 2: Education status in study population.

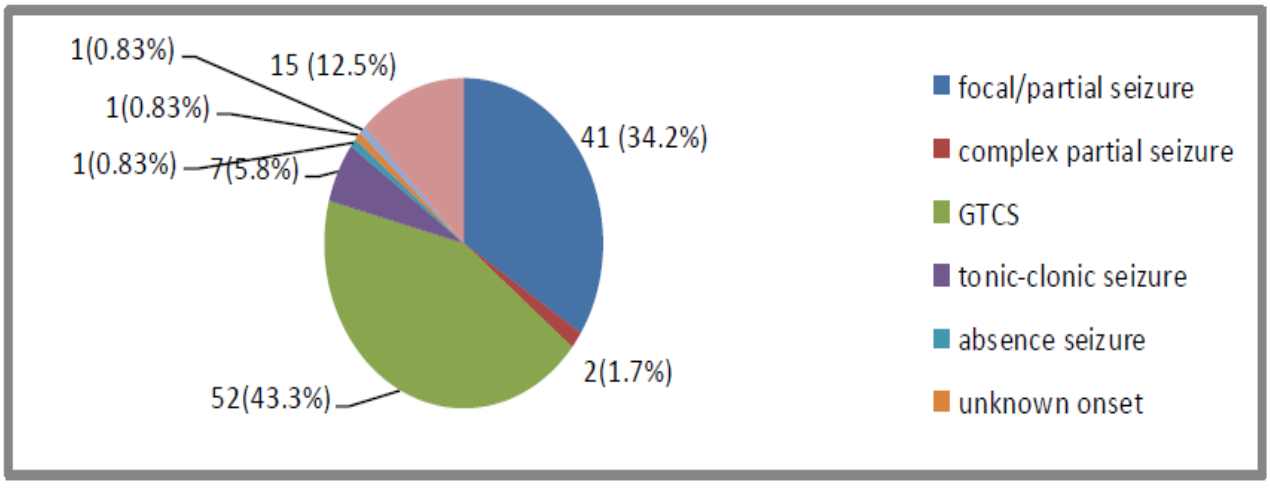

Figure 3: Types of epilepsy in study population.

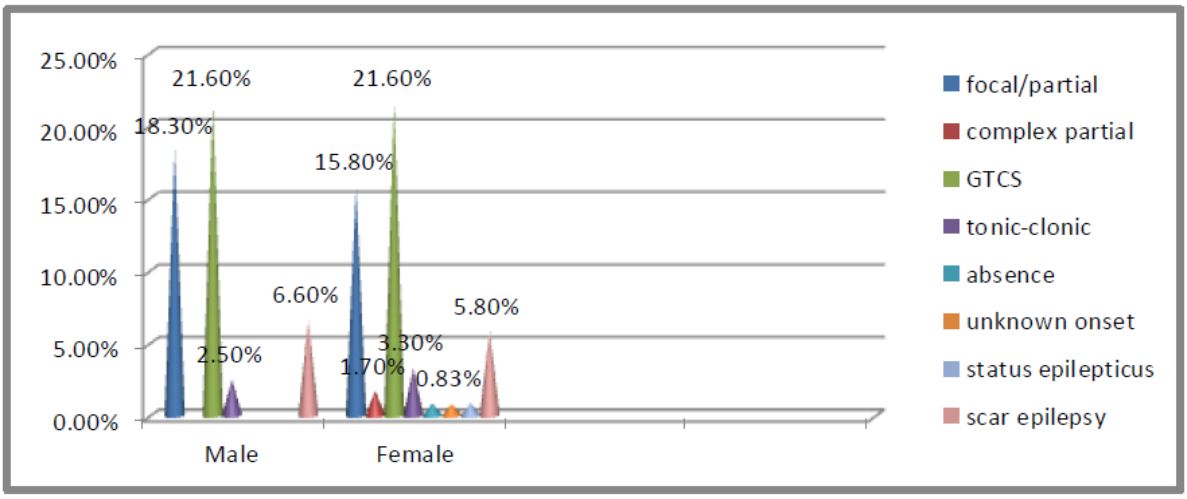

Figure 4: Types of epilepsy according to gender

PRESCRIBING PATTERN

Table 2: Type of therapy in study population.

Type of therapy	Frequency	Percentage
Single drug therapy	44	36.7
Two drug therapy	51	42.5
Three drug therapy	16	13.3
Four drug therapy	8	6.7
Five drug therapy	1	0.8

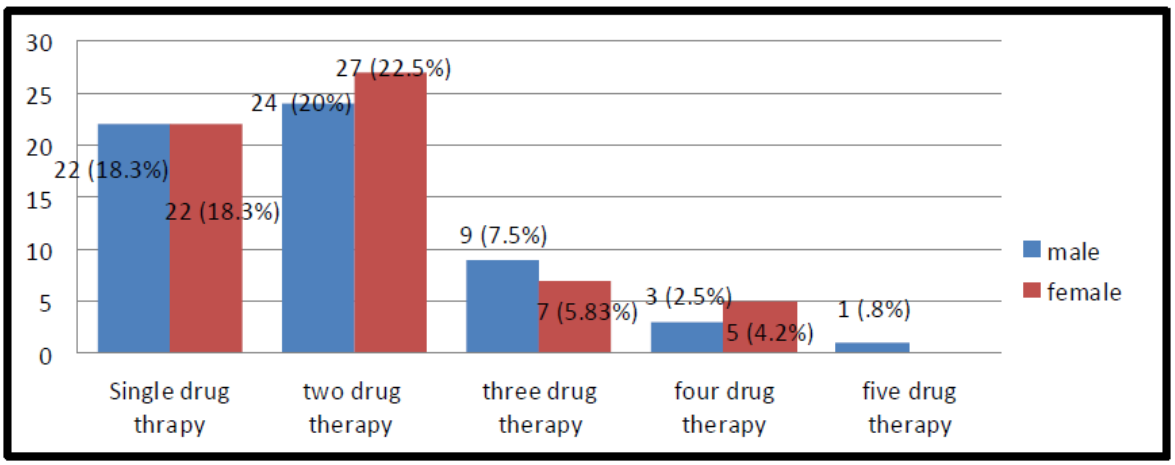

Figure 5: Type of therapy according to gender.

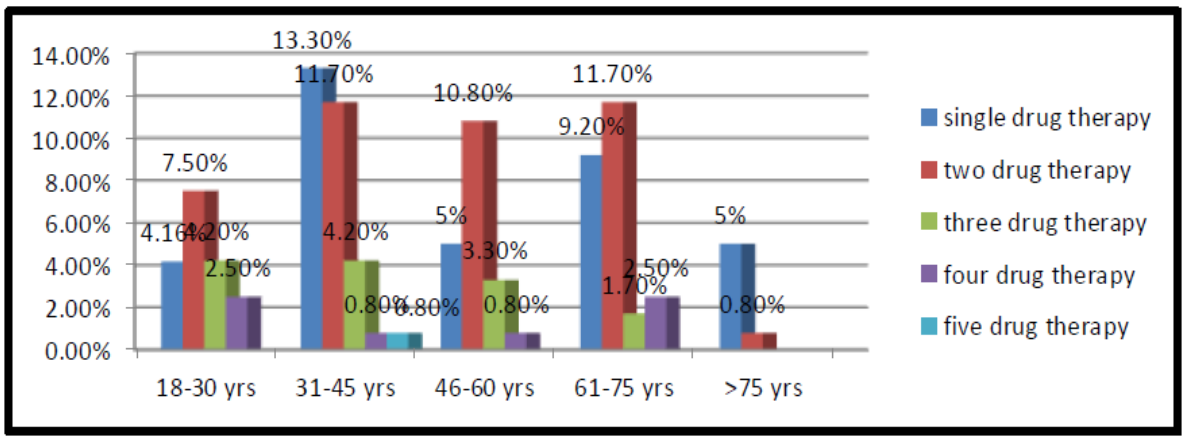

Figure 6: Type of therapy according to age group.

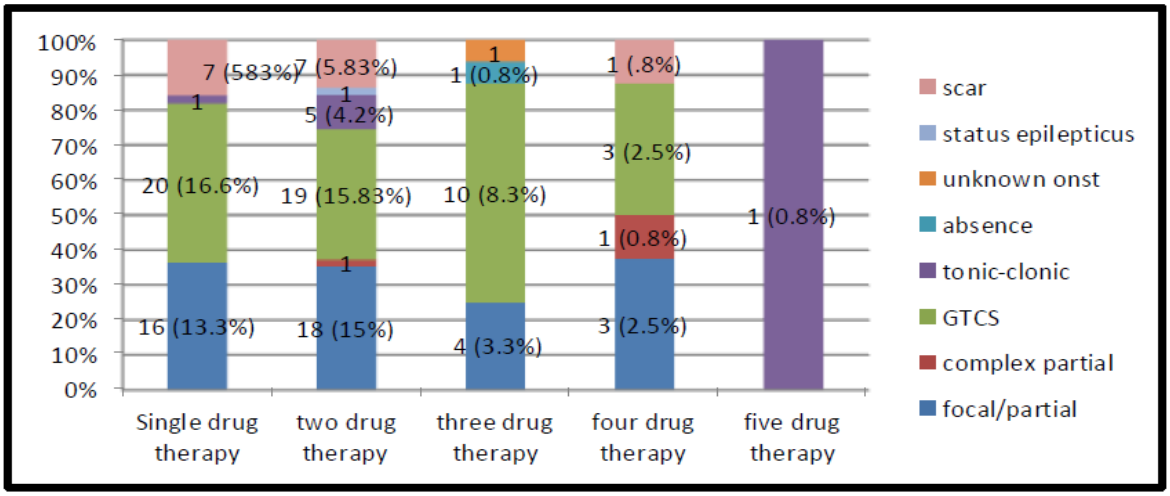

Figure 7: Type of therapy according to epilepsy type.

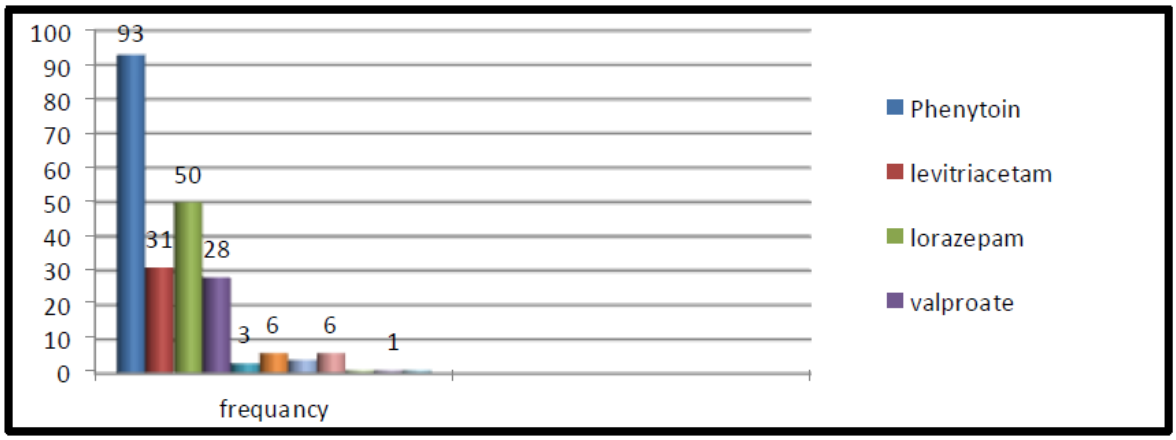

Figure 8: Overall AEDs utilization.

Table 3: Newer AEDs prescribed in study.

NEWER AEDs	FREQUENCY & PERCENTAGE (both mono and combinations)
Levetriacetam	31 (25.83%)
Pregabalin	1 (0.83%)
Oxecarbazepin	1 (0.83%)
Zonisamide	1 (0.83%)
Lacosamide	6 (5%)

ADRs

Table 4: Type of ADRs in study population.

Type of ADRs	Frequency	Percentage (n=120)	Male	Female	P value & pearson correlation
Skin rashes	7	5.8	5	2	
GI upset	5	4.2	3	2	
Gum bleeding	4	3.3	3	1	
Thrombocytopenia	5	4.2	2	3	
SJS	1	0.8		1	
Head ache	6	5	2	4	
Nystagmus	1	0.8	1		
Somnolence	3	2.5	1	2	
Hair loss	2	1.7		2	
Sedation	1	0.8		1	0.252 & 0.193
Hypotension	2	1.7	2		

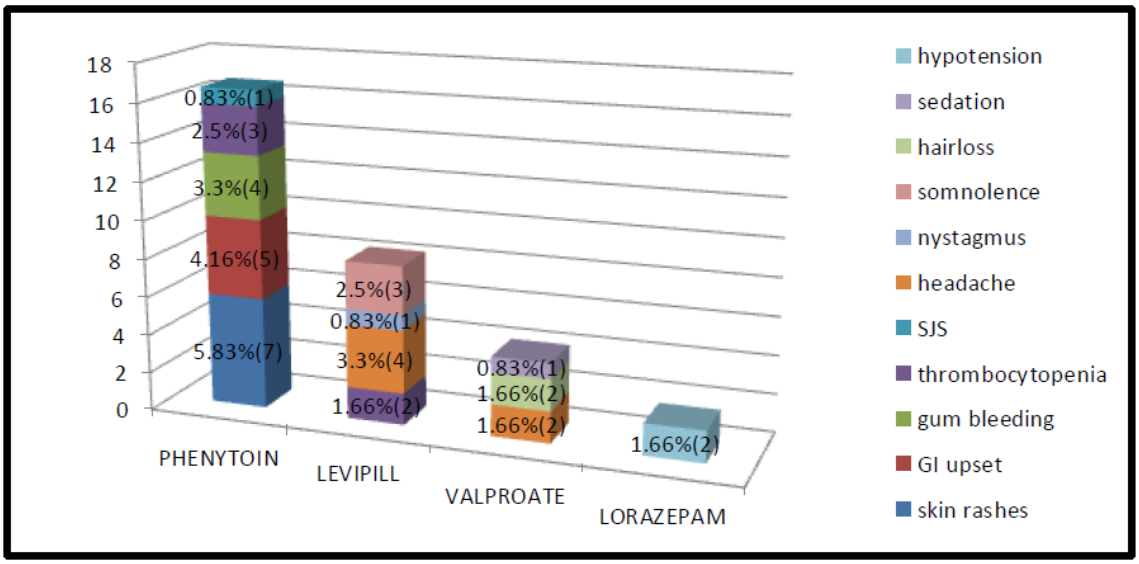

Figure 9: Type of ADRs according to AEDs.

Table 5: Causality assessment of ADRs

	Number	S.D
Definite	1	
Probable	14	16.356
Possible	22	16.090
Total	37	15.780

Table 6: Causality assessment of ADRs.

ADRs	Causality assessment	numbers	S.D	P value
Skin rashes	probable	5	12.857	
	possible	2	9.192	
GI upset	probable	3	13.856	
	possible	2	19.799	
Gum bleeding	probable	3	15.239	
	possible	1		
Thrombocytopenia	probable	1		
	possible	4	15.199	
SJS	definite	1		
Headache	possible	6	11.165	
Nystagmus	probable	1		
Somnolence	possible	3	8.737	
Hair loss	Possible	2	4.243	
Sedation	possible	1		
Hypotension	Probable	1		
	possible	1		

Table 7: Probable & possible AEDs causing ADRs.

	AEDs	Number of ADRs	Percentage (total no.of ADRs = 37)
Probable	Phenytoin Levitriacetam Lorazepam	11 2 1	29.7 5.4 2.7
	Phenytoin	8	21.6
Possible	Levitriacetam	8	21.6
	Valproate	5	13.5
	Lorazepam	1	2.7

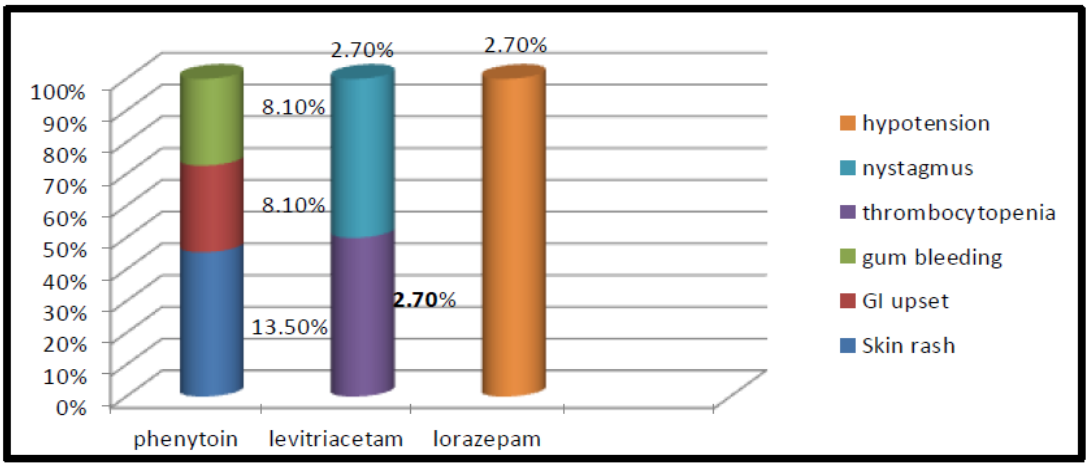

Figure 10: Types of ADRs with probable drugs.

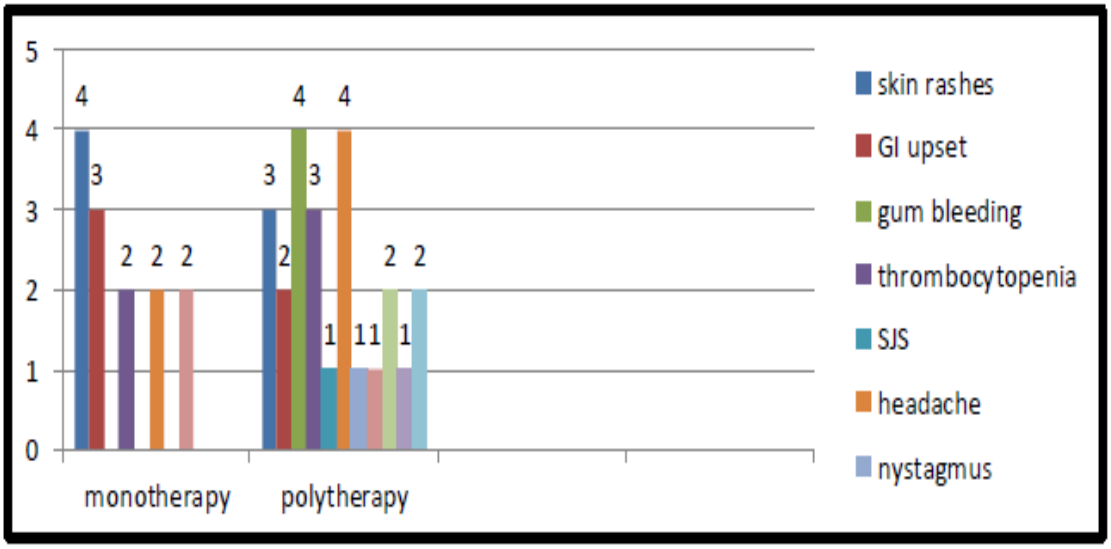

Figure 11: Influence of monotherapy & polytherapy on ADRs

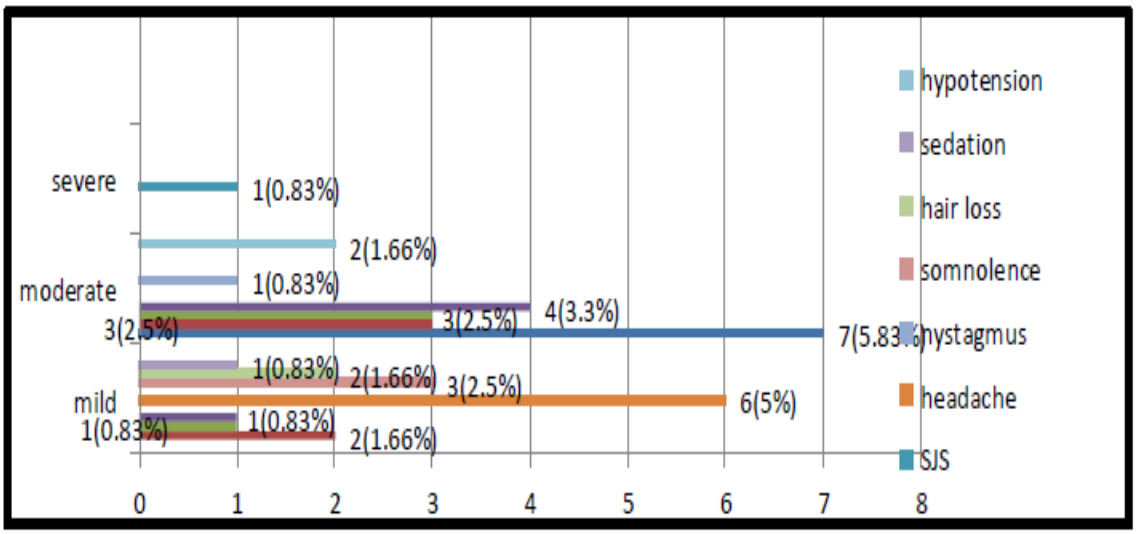

Figure 12: Severity assessment of ADRs.

MEDICATION ADHERENCE

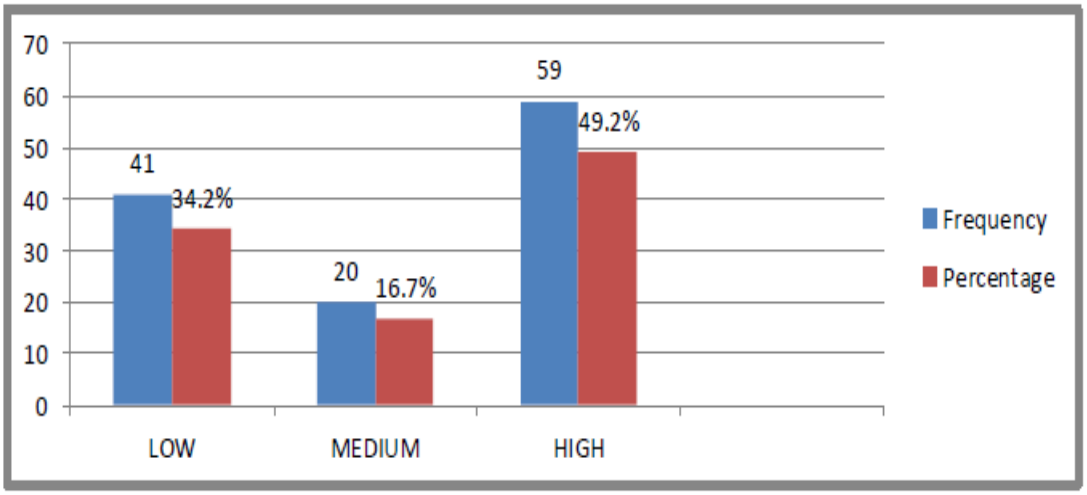

Figure13: Medication adherence in study population.

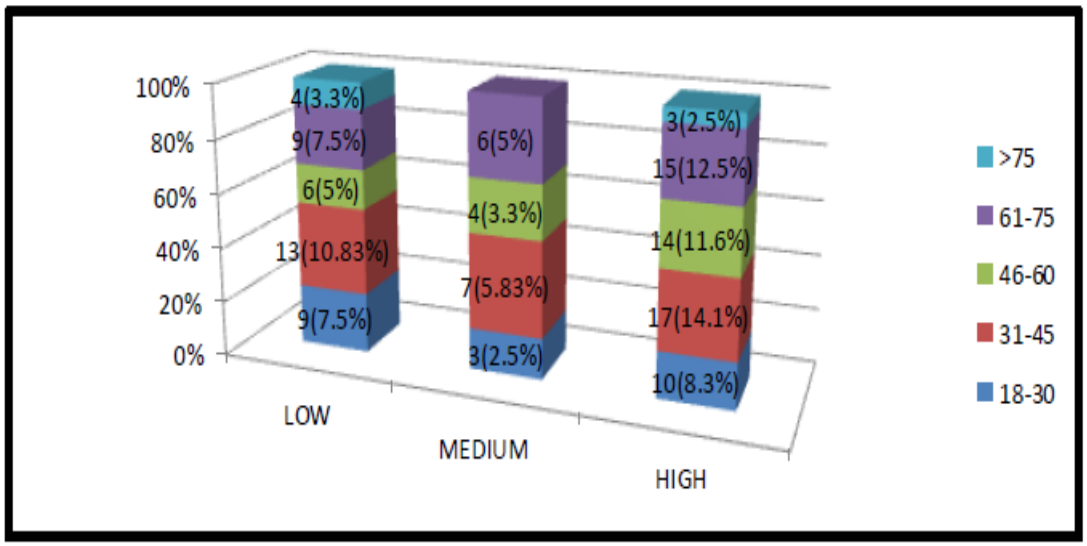

Figure 14: Medication adherence with age group.

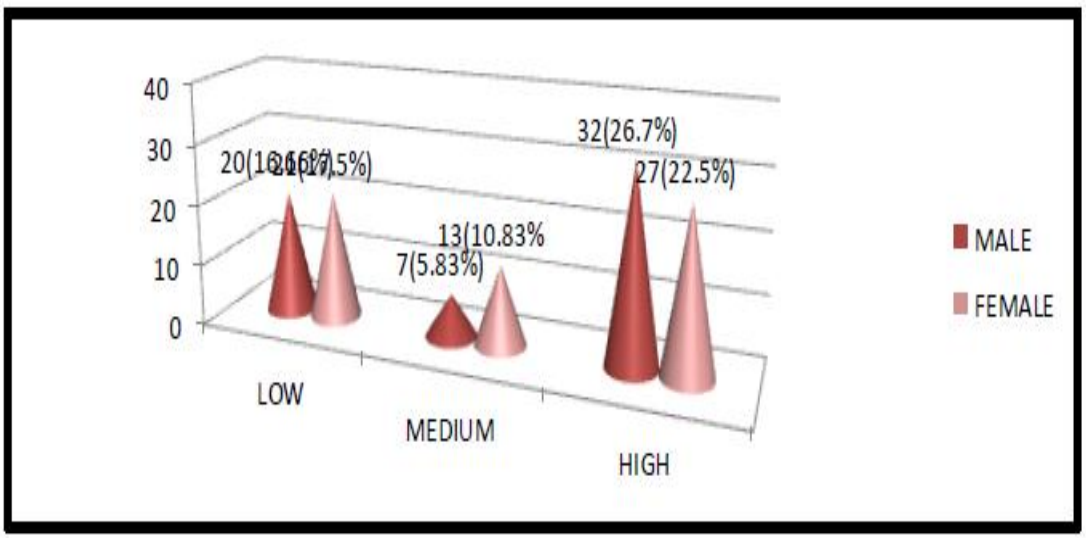

Figure 15: Medication adherence with gender.

Table 8: Medication adherence with education

Medication adherence	Education	Number	S.D	Percentage	Pearson correlation & p value
Low	illiterate	15	17.926	12.5	
	Primary	14	12.230	11.7	
	secondary	11	11.356	9.16	
	tertiary	1		0.83	
	total	41	19.753	34.2	
Medium	illiterate	5	4.219	4.16	
	primary	6	14.180	5	
	secondary	8	10.035	6.66	
	tertiary	1		0.83	
	total	20	16.742	16.66	
High	illiterate	9	8.471	7.5	
	primary	27	13.815	22.5	
	secondary	22	12.847	18.3	
	tertiary	1		0.83	0.163 & 0.076
	total	59	17.415	49.2	

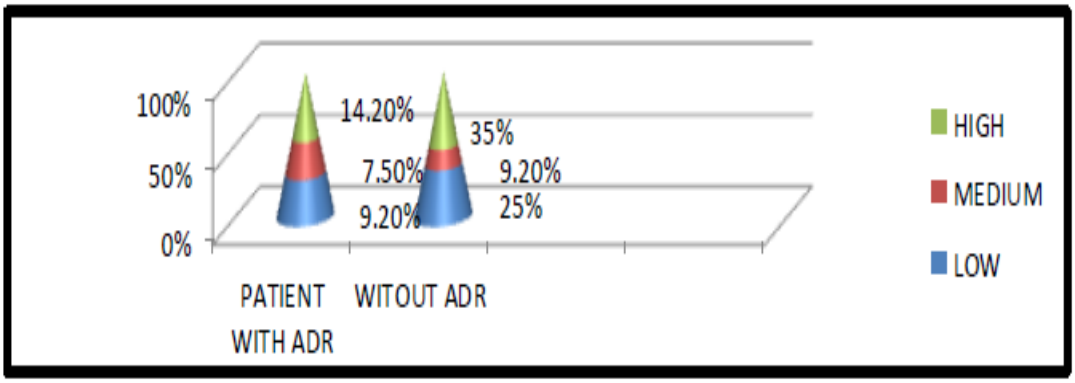

Figure 16: Medication adherence with ADRs.

Figure 1 shows that out of 120 patients, 49.2% were males (n=59) and 50.8% were females (n=61). Table 1 shows the 5 different age groups of patients, in that group of 31-45 year were the most frequent in number and >75 year group was less in numbers. In figure no 2; most of the patients were illiterate. In figure no: 3 & 4 shows types of epilepsy and its association with gender; GTCS and focal seizures were the most common epilepsy among the patients. Table no 2 shows type of therapy and figure no 5,6 & 7 shows type of therapy in accordance with gender, age group & epilepsy type. Most of the patients shows two drug therapy. Figure no 8 shows the overall AED utilization, in that phenytoin was the most commonly used AED. Table no 3 illustrate the newer AEDs used for the treatment of epilepsy. In that levitriacetam were prescribed mostly. Types of ADRs and its association with AEDs prescribed are expressed in table no 4 & figure no.9. Major ADRs were seen as skin rashes in 7 patients and least reaction was SJS. Table no. 5,6&7 and figure no.10 shows causality assessment of ADRs with AEDs by Naranjo causality assessment scale, 37.83% were probable, 59.46% were possible and 2.7% were definite respectively. The figure no 11 shows influence of mono and poly-therapy on ADRs. Polytherapy leads ADRs than monotherapy.The severity assessment was done by Hartwig severity scale, most of the ADRs were moderate (54.05%) and followed by mild 43.24% and 2.7% was severe. Figure no. 13, 14 & 15 shows medication adherence in accordance with age group and gender. 50.8% patients were not taking their medication properly. Table no. 8 shows medication adherence in accordance with education, most of the patientshave low education (24.2% uneducated, 39.2% primary educated), education is a factor for drug compliance. Also, ADRs is a factor for drug compliance, it shows in figure no.16.

DISCUSSION

The present study set out to analyze the prescribing pattern, compliance and adverse drug reactions with anti-epileptic pharmacotherapy in a tertiary care teaching hospital. It also aims to identify the severity of adverse drug reactions and how AEDs are prescribed for different types of epilepsy.

Out of 120 epilepsy cases reviewed, we found that female patients (50.8%, n=61) were predominant while comparing to male patients (49.2%, n=59) with an odds ratio of 1.427 (0.688 – 2.959). Out of the total study population, 30.8% (n=27) of patients belonged to the age group 31-45 years followed by the age group 61-75 years. The mean age of the population were found to be

49.03 years (SD +/- 18.024). The average age of the males were 51.22 years (SD +/- 18.025) comparing to females which was 49.90 (SD +/- 14.875). These result point out the maximum epilepsy incidence are seen in younger population. Generalized tonic-clonic seizures (GTCS, 43.3%, n=52) was found to be the major type of epilepsy followed by focal seizures (34.2%, n=41) and scar epilepsy (12.5%, n=15). Chi-square analysis showed that gender had a significant influence among various types of epilepsy with a p-value 0.023 (chi square value – 5.397).

Branded drugs (87.5%, n= 105) were the most prescribed drugs in study population followed by both generic and branded drugs (10.8%, n=13). Generic drugs are the drugs prescribed rarely in this study population (1.7%, n= 2). In the study population maximum (42.5%, n=51) of patients belonged to the two drug therapy followed by the therapies single drug therapy (36.7%, n=44) and three drug therapy (13.3%, n=16). The minimum (0.8%, n=1) of patients belonged to the five drug therapy. Age groups of 31-45 years (30.8%, n=37) were more using AEDs followed by age groups of 61-75 years (25%, n=30). In this study Focal seizures, GTCS, tonic-clonic and scar epilepsy may follows single, two drug three drug and four drug therapies, tonic-clonic seizures can follow five drug therapy also.

According to our study, the overall AEDs utilization was phenytoin (n=93, 77.5%, including both mono & combination therapy), levitriacetam (n=31, 25.8%), lorazepam (n=50, 41.7%), valproate (n=28, 23.3%), carbamazepine (n=3, 2.5%), phenobarbitone (n=6, 5%), benzodiazepine (n=4, 3.3%), lacosamide (n=6, 5%) and zonisamide, oxecarbazepine & pregabalin (n=1, 0.83%). We found that phenytoin, levitriacetam, valproate and phenobarbitone were commonly prescribed as mono-therapy. Other drugs were prescribed in combination with phenytoin, levitriacetam and valproate. In our study, we found that levitriacetam (25.83%), pregabalin (0.83%), oxecarbazepine (0.83%), zonisamide (0.83%) and lacosamide (5%) are the newer AEDs prescribed to treat epilepsy. According to our study, levitriacetam was the most commonly used newer AED followed by lacosamide. In this study population phenytoin (77.5%) was most prescribed anti-epileptic drugs. The polytherapy is needed to treat epilepsy. In this study most commonly prescribed two drug therapy was phenytoin + lorazepam (n=21), three drug therapy was phenytoin + levitriacetam + lorazepam (n=5), and four drug therapy was phenytoin + levitriacetam + lorazepam + valproate (n=3). The commonly prescribed AEDs were phenytoin, levitriacetam, valproate and lorazepam, prescribed as mono-therapy as well as polytherapy.

Among 120 patients, 30.83% (n=37) patients were observed with adverse drug reaction. We found that male patients (51.4%, n=19) were predominant while comparing to female patients (48.6%, n=18). The correlation between patients observed with ADRs and gender was found to be 0.029 with a P value of 0.752 whereas, the correlation between reported ADRs and gender was found to be 0.193 with a P value of 0.252. Higher incidence of ADR were observed in the age group of 31-45 years (n=15, 40.5%/37 ADRs reported). According to our study, skin rashes (5.8%, n=7 out of 120 patiens) was the mostly seen adverse reaction and rarely seen adverse reaction is stevens-johnson syndrome (SJS) and nystagmus (0.8%, n=1/120 patients). Other reported adverse reactions include, gastrointestinal upset (4.2%, n=5), gum bleeding (3.3%, n=4), thrombocytopenia(4.2%, n=5), headache (5%, n=6), somnolence (2.5%, n=3), hair loss (1.7%, n=2), hypotension (1.7%, n=2) and rarely sedation (0.8%, n=1). Among 120 patients, 37 ADRs were reported, maximum ADRs (16.66%, n=20) were induced by phenytoin followed by levitriacetam (8.35%, n=10) and minimum ADRs induced by lorazepam (1.7%, n=2). The common ADRs induced by phenytoin was skin rashes (n=7) and the severe ADRs induced by phenytoin was SJS (n=1). Among 37 reported ADRs 37.83% (n=14) of probable category while 59.46% (n=22) ADRs were possible category, while only the SJS were definite category (2.7% n=1). 43.24% (n=16) ADRs were mild, 54.05% (n=20) were moderate and 2.7T% (n=1) ADR were severe. The severe ADR include stevens-Johnson syndrome. According to study, we can found that phenytoin can cause mild, moderate and severe ADRs while levitriacetam and valproate cause only mild and moderate ADRs. To treat epilepsy, polytherapy was most preferred than mono-therapy. But polytherapy is more susceptible to causing ADRs than mono- therapy.

Totally 120 patients were assessed, 49.2% were compliant the medication while 50.8% were incompliant. According to the study, 63.3% of the patients stated education as the reason for non-compliance. The correlation of medication adherence with education was found to be 0.163 with a P value 0.076. In this study, 55.7% (n=34) female patients shows more drug incompliance than male 44.3% (n=27). The correlation between medication adherence and gender is 0.058 with a P value of0.527. The age group 31-45 years shows more drug incompliance 32.8% followed by 61-75 years (24.6%) and the correlation of adherence with age group was found to be 0.027 with a P value of 0.383.The adherence level was assessed by using validated Morisky green test. In our study 16.7% had medium and 34.2% had low adherence. Out of 120 patients, 49.2% (n=59) patient forget to take their medicine and 32.5% (n=39) were careless to take their medicine. The study found that illiteracy was the main cause of drug incompliance. In our study, majority of the sample did not experience any adverse reactions, that is among 120 patients, 83 patients did not experience any adverse reactions whereas 37 patients experience side effects. Out of 37 ADRs reported, 11 (9.2%) patients shows low medication adherence, 9 (7.5%) patients shows medium medication adherence and 17 (14.2%) patients shows high medication adherence. It shows that presence of

side effects may influence the drug compliance in patients.

CONCLUSION

The AEDs of choice for different seizures were accordance with the recommended guidelines. Our study reveals that the generalized tonic-clonic seizure is the commonest type of epilepsy recorded. In our study we found that poly-therapy is the most drug of choice in most of the epileptic patients. Phenytoin and levitriacetam are the most commonly used mono-therapy. Our study reveals that the conventional AEDs are commonly used. The use of newer AEDs is still minimal. This may be because of lack of experience in using newer AEDs.This study analyses the ADRs associated with anti-epileptic; the poly-therapy is the most preferred therapy pattern for epileptic patients, this indicates that the epileptic patients should be closely monitored for ADRs, to avoid clinically significant harmful consequences.

According to our study, majority of the patients found to be compliant. Drug compliance is found to be influenced significantly by the factors like education, duration of illness, side effects, type of therapy, frequency of medication. In our study, we found that illiteracy is the most common cause for non-compliance and female patients are more drug incompliant than male patients. Most of the patients were skipping their medications either due to carelessness or lack of memory. The study was conducted to measure drug compliance and to identify the major factors influencing drug compliance which helped in counseling the patients appropriately and thus helped in reducing non-compliance nature in epilepsy patients.

Pharmacists are important health professionals in counseling and monitoring the patients with epilepsy. They have significant role in education of patients about the disease and therapy, encouraging adherence and explaining side effects and providing information on potential drug- drug interactions, resulting in improved clinical outcomes, reduce the risk of adverse reactions and decreased costs. Moreover, pharmacist can help prevent the progression of co-morbidities and it improves the patients quality of life and agility in daily activity. However, there are certain challenges which the pharmacist should overcome, that is, the gap between views of patient and pharmacist has to be narrowed to ensure enhanced role of pharmacist in patient group.

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