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DRUG UTILIZATION EVALUATION ON ANTIEPILEPTIC DRUGS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Newer antiepileptic drugs are becoming available now and how these drugs are utilized is very interesting to see. Problems in antiepileptic therapy like use of poly-therapy, adverse drug reactions, drug interactions, lack of adherence to medications etc., can be identified and resolved by clinical pharmacist. Considering all these facts we started study on drug utilization of antiepileptic drugs in tertiary care hospital. **Materials and Methods:** Prospective observational study of 7 months duration from September 2019 to March 2020 was carried out after human ethics research committee approval. All in-patients prescribed with anti-epileptic drugs in Pediatric & General medicine department were selected. Data were collected in customized data collection form after taking patient consent and also from patient case sheets/prescriptions. Morisky Medication Adherence Scale-8 questionnaire was used to assess the adherence at baseline. Data were measured in percentage and frequency using descriptive statistics. Microsoft office was used to summarize the analysis of data. **Results:** A total of 120 patients enrolled to study where 209 antiepileptic drugs were prescribed. Females (58%) and patients with age group of 0-18 years (58.33%) were more exposed to these drugs. 80% of diagnosis was epilepsy without any co-morbidity. Prescription pattern of drugs showed that Phenytoin (34.44%) was the most common drug used either as single or in combination with other drugs to treat several of indication. At maximum 4 antiepileptic drugs were seen in one prescription introducing poly-therapy (64.16%). We have seen very less (3.82%) prescriptions for newer compared to older generation anti-epileptics. Among total 82(68.3%) drug interactions which were identified, 43.9% were severe, 39.02% were mild and 17.073% were moderate ones. We have also seen 66.66% of patient were having poor medication adherence score at baseline. We counselled these patients. All interventions were accepted by physician. **Conclusion:** Very less new antiepileptic drugs were used with high evidence of poly-therapy. Phenytoin was the most commonly prescribed drug. Clinical pharmacist mediated services helped to identify and reduce drug therapy related problems.

KEYWORDS: Anti-epileptics drug, prescribing pattern, poly-therapy, drug interaction.

INTRODUCTION

Drug utilization is defined by World Health Organization (WHO) as the study of marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences. Drug utilization research helps in identification of clinical use of drugs in populations and its impact on healthcare system.

1. The aim of drug utilization study is to improve rational use of drugs in populations. For the individual patient, rational use of a drug implies the prescription of a well-documented drug in an optimal dose on the right indication, with the proper information and at a low-cost price. Without knowledge on how drugs are being prescribed and used, it is difficult to initiate a decision on rational drug use and to suggest measures to change prescribing habits for the better. Information on the past performance of prescribers is the essential of any auditing system. Drug utilization study in itself does not necessarily provide answers, but it contributes to rational drug use.

2. Continued clinical usage for many decades, some head to head randomized double blind trails, many open label randomized trials and post marketing trials have represents the profiles of traditional antiepileptic drugs (AEDs). So there is need to perform drug utilization studies.

3. Epilepsy is the most common neurological condition worldwide with Indian prevalence of 572.8/100,000 population/year. This shows rising trends as treatment gaps for active epilepsy exceeded 75% in most low-income countries. Peoples may expose to different anti-epileptics. So there may be differing trend of utilization of anti-epileptics.
4. The main stay of management of epilepsy is anti-epileptics.
5. There are two different types of anti-epileptics i.e. older and newer generation. The older (traditional) AEDs included Phenobarbital, Phenytoin, Primidone, Ethosuximide, Benzodiazepines, Carbamazepine andValproate, while the newer AEDs has the list of Felbamate, Gabapentin, Lamotrigine, Pregabalin etc.
6. New AEDs have been marketed during the last 20 years. There is still a lack of documentation of safety aspects regarding many of these drugs, as the use in special patient populations like children, women of child bearing age, and elderly.
7. Apart from epilepsy; AEDs are also used to treat multiple non-epilepsy disorders like neuropathic pain, migraine, essential tremor, spasticity, restless legs syndrome, bipolar disease, schizophrenia, and anxiety disorders in which both classic and newer AEDs may be used. Correspondingly, in traumatic brain injury, Parkinson's or Alzheimer's disease, alcohol abuse and obesity also anti-epileptics are utilized.
8. Until recently, only a limited number of anti-epileptic drugs were available and all had troublesome side effects. There have been several new AEDs launched since 1990. Newer AEDs are mainly used as additional treatment in people whose epilepsy is not well controlled on older AEDs alone. Newer AEDs are promoted as effective as older drugs but with less side effects.
9. Despite more than 20 approved antiepileptic drugs, about 30% of patients are refractory to treatment. An important characteristic of pharma-co-resistant epilepsy is that most patients with refractory epilepsy are resistant to several, if not all, AEDs, even though these drugs act by different mechanisms. Pharma-co-resistant epilepsy is a major health problem, associated with increased morbidity and mortality, and accounting for much of the economic burden of epileptic patients.
10 Population-based studies of drug utilization demonstrate that 19-24 % of patients with epilepsy use poly-therapy with AEDs. In recent studies of children and adults with refractory epilepsy, 64% used poly-therapy with two or more AEDs, and 35% of the adults suffered from CNS-related comorbid conditions, resulting in a considerable risk of interactions. Poly-therapy and the potential for interactions with other drugs increase with increasing age, and the elderly is the largest group with new onset epilepsy having a considerable risk of interactions with commonly prescribed drugs other than epilepsy, including migraine, neuropathic pain, bipolar disorder, anxiety, and many other disorders.
11 More studies are required to evaluate their use as first line AEDs for children with epilepsy. Caution must be exercised for possible drug interactions with conventional AEDs before using them as an adjunct.
12 Nowadays, the WHO definition of adherence has been universally accepted; the extent to which a person's behavior – taking medication, following a diet, and or executing lifestyle changes – corresponds with the agreed recommendations from a provider. This definition highlights the importance of an active involvement of the patient with the health professionals with a good communication. In developed countries, non-adherence to the treatment of chronic diseases ranges from 30% to 50%, and this rate is even higher in developing countries.
13 Most interesting is that 60% of treated adults stop taking medication without relapse within 2-5 years of treatment. The adherence behavior of patient can be increased to effectively manage the epilepsy.
14 A survey undertaken by Neurologists in the USA revealed that 71% of patients with Epilepsy forgot to take their AED (anti-epileptic drug) at least once per month and the chance of a patient missing a dose increased with the number of tablets prescribed. Of patients that missed a dose 45% reported a seizure. Similar results were reported in a recent UK study which revealed that 59% of epilepsy patients had poor compliance and that this was related to an increased frequency of seizures. Non-compliance significantly increases the risk of seizure, A&E visits, hospitalization, road traffic accidents, fractures and death and is therefore key contributor to suboptimal management.
15 Poor patient adherence to medication is one of the most common causes of increased morbidity and mortality. Lack of adherence has been estimated to cost the U.S. health care system between $100 billion and $289 billion annually in direct costs. Many studies are carried out to examine the current situation of medication adherence, its predictors, its relationship to patient outcomes and ways to improve it. Therefore, finding accurate and standardized measurements of medication adherence is of great importance.
16 Antiepileptic medication should not be prescribed without a careful evaluation of the risks and benefits of treatment and a discussion with the individual patient about the merits and potential side effects of treatment. Most patients with epilepsy will become seizure-free with appropriate antiepileptic drug (AED) treatment and will then be reviewed by primary care services.
17 Other set of problems in anti-epileptics are: adverse drug reactions (ADRs) and drug interactions. These are major clinical problems in both pediatrics and adult medicine. Systematic reviews and meta-analyses of prospective studies of drug surveillance in children have showed that one in 10 children in hospital will experience an ADR. One in every 500 children will experience an ADR each year. There are significant ADRs in association with the newer AEDs. Additionally, the reporting of drug toxicity in clinical trials of AEDs is poor.
18 In a recent Cohort study at 1998, the risk for "AED hypersensitivity syndrome" (AHS), which is characterized by the triad of fever, skin rash, and single

or multi-organ system involvement in first-time users of PHT or CBZ was estimated at 2.3-4.5/10,000 and 14.1/10,000 patients, respectively. However, up to 3 1 % of patients receiving AED therapy may complain of one or more ADRs, as shown in a recent multicenter survey.
19 A study carried out in 2014, it was found that up to 61% of patients taking conventional AEDs, such as Phenytoin, Carbamazepine, Valproate and Phenobarbital may give rise to unexpected ADRs like cutaneous reaction and serious hematological disorder, central nervous system (CNS) abnormalities, or hepatic failure. Most of these disorders are related to toxic metabolic products of AEDs which are thought to contribute to initial treatment failure in up to 40% of patient.
20. Antiepileptic drugs show clinically significant interactions both with each other and with other medications, because of the specific pharmacokinetic profile and relatively narrow therapeutic range. Unpredicted changes of the patient's clinical condition with the controlled dosage are mainly caused by the occurrence of interactions.6 There are two types of drug interactions between drugs such as pharmacokinetic and pharma-co-dynamic. For AEDs, pharmacokinetic interactions are the most notable type, but pharma-co-dynamic interactions involving reciprocal potentiation of pharmacological effects at the site of action are also important. By far the most important pharmacokinetic interactions are those involving cytochrome P450 iso-enzymes in hepatic metabolism.5 When multiple drug therapy is used, there is a possibility of clinically relevant drug interactions, which in patients with epilepsy are particularly common for a variety of reasons.
1) AEDs are administered for prolonged periods, often for a lifetime, thereby increasing the probability of co prescription.
2) Most AEDs have a narrow therapeutic index, and even relatively modest alterations in their pharmacokinetics can result in loss of response or toxic effects.
3) The most widely used AEDs (carbamazepine, valproic acid, phenytoin and phenobarbital) have prominent effects on the activity of enzymes which metabolize the majority of existing medication.
4) Most of the old and new generation AEDs are substrates of the same enzymes.
21. Developing countries have limited funds available for health care and drugs so it becomes very important to prescribe drugs rationally so that the available funds can be utilized optimally. More studies are required to evaluate their use as first line AED for children with epilepsy, caution must be exercised for possible drug interactions with conventional AEDs before using them as an adjunct.
22 The interest in drug utilization studies began in the early 1960s and its importance has increased since then due to increase in marketing of new drugs, wide variation in the pattern of drug prescribing and consumption, growing concern about delayed adverse effects and the increasing concern regarding the cost of drugs.
23 As drug utilization studies serve as a mean to interpret, intervene and promote the rational prescribing, dispensing and administration of medication. Thus, the ultimate outcomes of DUR are: improved quality of patient care, better therapeutic outcomes and cost effective pharmacotherapy.7 The study was undertaken to know the drug usage pattern in epileptic patients.

OBJECTIVES

PRIMARY OBJECTIVE

To study the drug utilization pattern of antiepileptic drugs in rural tertiary care teaching Hospital.

SECONDARY OBJECTIVES

To identify the common class of drugs prescribed and indication for therapy.
To assess the adverse drug reactions of prescribed drugs.
To assess and identify the potential drug interactions.
To identify the extent of polytherapy with antiepileptic drugs in enrolled patients
To study the medication adherence behavior among enrolled patients.

METHODOLOGY

➔ ***STUDY FLOW CHART***

Obtained permission from Institutional Ethical Committee.

⇩

Preparation of patient data collection form, questionnaire and consent form.

⇩

Enrolling the inpatients and Collection of data.

⇩

Documentation of data

⇩

Evaluation/analysis of collected data for assessment of pharmaceutical care.

STUDY DESIGN- The study was a prospective and observational study.

STUDY PERIOD- This study was conducted for a period of 7 months.

STUDY APPROVAL.- Ethical clearance was obtained from the Institutional Ethical Committee.

STUDY CRITERIA

Inclusion Criteria

All in-patients both sex prescribed with anti-epileptic drug in Pediatric & General medicine departments In-patients who are willing to participate in the study.

Exclusion Criteria: Pregnant/lactating women.

SOURCE OF DATA

- ➔ Patient data relevant to the study was obtained from the following sources
- ➔ Patient consent form
- ➔ Patient data collection form
- ➔ Patient case note/prescription
- ➔ Lab reports
- ➔ Morisky medication adherence scale questionnaire.

STUDY PROCEDURE

In-patients who met the study criteria were enrolled to the study for assessing drug utilization pattern after obtaining their written consent from patient/patient care taker in medicine units & pediatric units. A suitably designed data collection form was used to record all the necessary data including patient demographic details, patient medication history, and reason for admission, medication details and lab investigations.

ADR and Drug Interactions

The enrolled patient's (inpatients) case sheet was reviewed every day during ward round participation. Serious/major drug-drug interactions and Adverse Drug Reactions (ADRs) were identified by using standard text books like Harrison's principles of internal medicine 16th edition, Martindale the complete drug reference thirty-sixth edition, and MICROMEDEX softwares available in the department. The identified drug related problems were discussed with the physicians for further management. Morisky medication adherence scale questionnaire: An 8 item adherence scale of Morisky DE was used and prior permission was taken before conducting the study.

➔ Morisky Medication Adherence Scale questionnaire.

For every answer response of NO scored as 1 and for YES scored as 0 (questions 1, 2, 3, 4, 6, 7) and to reverse the code response in a positive direction for item 5 and standardize the code for item 8 (0-4), resulting in a scale from low adherence to high adherence. Item 8 is divided by 4 when calculating summated scores, like item 8=4 – 1, item 8=3 -0.75, item 8=2 – 0.50, item 8=1 – 0.25 and item 8=0 – 0 respectively.

STATISTICAL METHODS

The data were subjected to descriptive statistical analysis using Microsoft office.

Microsoft word and Excel have been used to generate bar graph, pie charts and tables.

RESULTS

A total of 120 patients admitted to pediatrics and medicine units prescribed with various antiepileptic drugs were reviewed over a period of 7 months from September 2019 - March 2020.

DEMOGRAPHIC DETAILS

Table 1: Gender distribution and Age distribution.

Demographic details	Frequency(N)	Percentage (%)
Male	50	41.66%
Female	70	58.33%

Demographic details	Frequency(N)	Percentage (%)
0 -18	70	58.33%
19 – 35	13	10.83%
36 - 60	22	18.33%
61 – 80	14	11.66%

Table No.1: Demographic details of patient: It showed that more pediatric patients (age group of 0-18) than adults and geriatric cases. (> 18 age group) were included in our study as shown in table.

Females were more (58.33%) than male patients (41.66%).10.83% of people was within 19-35 age groups, 18.33% of people were within age group of 36-80 and 11.66% of people were within age group of 61-80. 58.33% of people were with age group of 0-18.

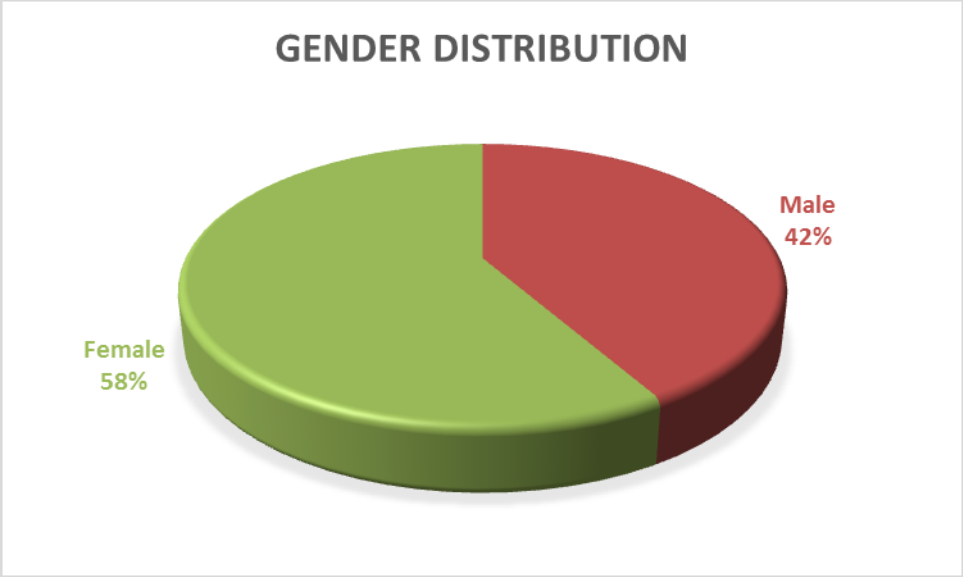

Figure No.: Gender wise distribution of patients.

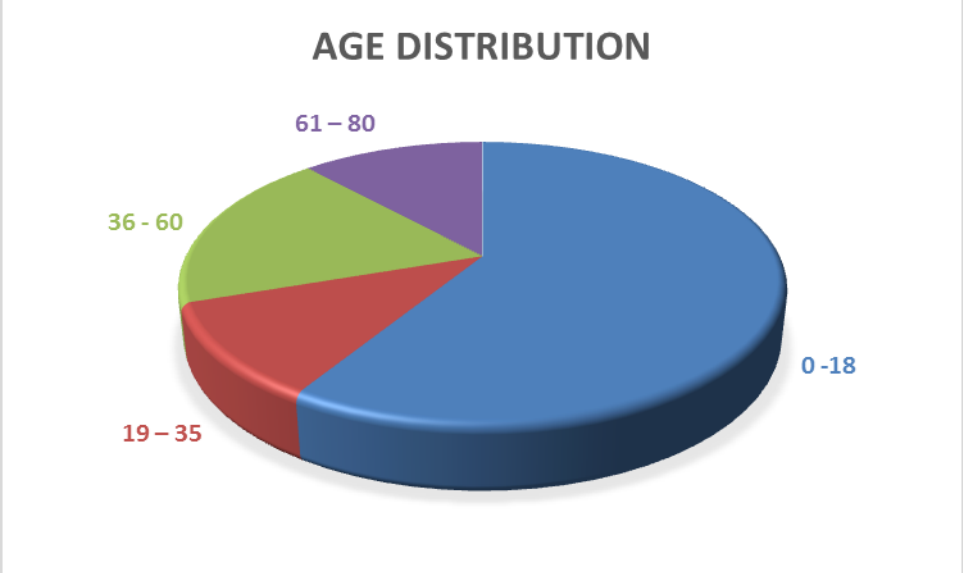

Figure No.: Age wise distribution of patients.

Table No.2.

Diagnosis	Frequency (N)	Percentage(%)
Epilepsy without co-morbidity	96	80%
Epilepsy with co-morbidity	24	20%
✓ Hypertension, Diabetes Mellitus	9	7.5%
✓ Cardiovascular accident,Hypertension,Diabetes melleitus	5	4.166%
✓ Meningitis	5	4.166%
✓ Alcohol withdrwal symptom	2	1.66%
✓ Viral fever and seizure	1	0.833%
✓ Migraine	1	0.83%
✓ Bronchopneumonia	1	0.83%

Table No.2: It showed that out of 120 patients 96(80%) were having epilepsy without any co- morbid condition and 20% were having co-morbidities like Hypertension(HTN) plus Diabetes mellitus (DM) (7.5%), Cardiovascular accident plus Hypertension plus Diabetes mellitus (4.1%), Meningitis (4.1%), Alcohol withdrawal symptom (1.66%) and Viral fever (0.83%), Migraine (0.83%), Bronchopneumonia(0.83%).

Table No.3: Distribution of Epilepsy.

Different forms of epilepsy	Frequency	Percentage (%)
Status epilepticus	9	7.5%
Partial Siezure	5	4.16%
Generalised tonic clonic siezures	44	36.6%
Generalised tonic clonic siezures by hot water	16	13.33%
Generalised tonic clonic siezures by alcohol dependence	3	2.5%
Fibrile seizures	16	13.3%
Atypical seizures	8	6.66%
Typical seizures	17	14.16%
Focal seizures	2	16.66%
Total	120	100%

Table No.3: It showed that generalized tonic clonic seizures (36.6%) followed by Atypical seizures (6.66%) Typical seizures (14.16%), Status epilepticus(7.5%), Partial Siezure (4.16%), hot water epilepsy (13.33%), alcohol dependence and Focal seizures (2.5%) were the different types of epilepsy encountered in our hospital.

Table 4a: Indication wise utilisation pattern of drugs and polytherapy.

Indication	Utilisation pattern of antiepileptics	Frequency(N) of patients	Status of polytherapy
Status Epilepticus	Phenytoin+Lorazepam	1	Polytherapy
	Phenytoin +Lorazepam+ Clobazam	1	Polytherapy
	Phenytoin + Phenobarbital	1	Polytherapy
	Phenytoin Only	2	Monotherapy
	Phenytoin +Valproate	1	Polytherapy
	Phenytoin +Levetiracetam+ Phenobarbital+ Midazolam	1	Polytherapy
	Phenytoin + Levetiracetam+ Midazolam	1	Polytherapy
	Phenytoin + Lorazepam + Phenobarbital	1	Polytherapy
			Monotherapy=2,Polytherapy=7
Partial Seizure	Phenytoin +Clobazam	1	Polytherapy
	Levetiracetam	1	Monotherapy
	Phenytoin +Valproate	1	Polytherapy
	Carbamazepine +Levetiracetam	2	Polytherapy
			Monotherapy=1,Polytherapy=3
Generalised Toinic Clonic Seizures	Phenytoin + Carbamazepine+Lorazepam	1	Polytherapy
	Phenytoin +Carbamazepine	11	Polytherapy
	Phenytoin + Carbamazepine+Phenobarbital	1	Polytherapy
	Phenytoin	9	Monotherapy
	Phenytoin + Phenobarbital	3	Polytherapy
	Phenytoin + Clobazam	2	Polytherapy
	Phenytoin +Lorazepam	12	Polytherapy
	Phenyoin+Lorazepam + Clobazam +Levetiracetam	1	Polytherapy
	Phenytoin + Carbamazepine+ Clobazam	1	Polytherapy
	Phenytoin + Clobazam+ Valproate	2	Polytherapy
			Monotherapy=9,Polytherapy=10
Focal	Phenytoin + Lorazepam	1	Polytherapy

Seizures			
	Lorazepam	1	Monotherapy
			Monotherapy=1,Polytherapy=1

Table 4a: Showing indication wise utilization pattern of drugs and status of poly-therapy of patients. In GTCs which accounts for frequent diagnosis; phenytoin 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 1st drug introducing polytherapy. All the time phenytoin and another anti-epileptic drug combination were used as polytherapy except in one case where clobazam and midazolam was also used to treat GTC. Most commonly used add on antiepileptic was lorazepam followed by carbamazepine, phenobarbital, clobazam with phenytoin which introduced polytherapy. At maximum upto 4 different antiepileptic drugs were used to treat different indication. Dugs utilized to treat indications other than GTCs were as shown. Overall the status of polypharmacy was as shown below.

Table 4b.

Number of antiepileptic drugs per prescription	**Frequency (N)**	Percentage (%)	**Total**
Monotherapy :			
1	43	35.833%	35.833%
Polytherapy :			
2	62	51.66%	64.16%
3	13	10.83%	
4	2	1.666%	
Total =	120	100%	100%

Table 4b: It showed that majority of cases, antiepileptic drugs were used as poly therapy other than monotherapy. Overall 43 (29.86%) patients treated by monotherapy i.e. 1 antiepileptic dugs and 78(63.33%) patients were treated with 2 or more than 2 drugs i.e. polytherapy. Among the patients who got polytherapy, 61 patients got 2 antiepileptics, 13 patients got 3 antiepileptics and 2 patient got 4 antiepileptics drug treatment.

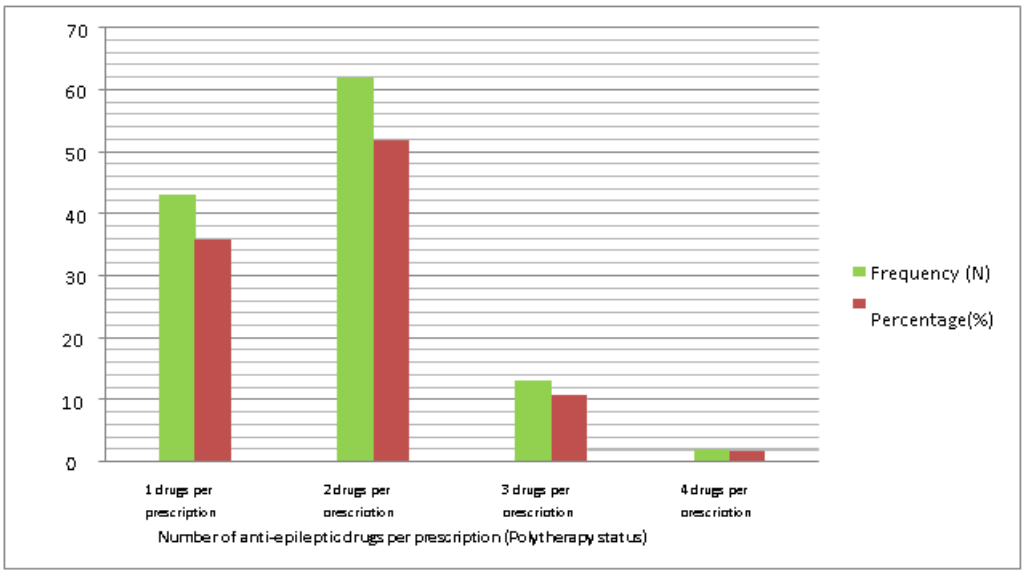

Figure 3: It showed utilization of number of antiepileptic drugs per prescription. Overall poly therapy (64.16%) strategy was used more than monotherapy status (35.833%). 2 drugs per prescription were more than 3 or 4 drugs per prescription respectively.

Table No.5: Extent of Antiepileptic Drug Utilization.

Drugs	Frequency (N)	Percentage (%)
Phenytoin	72	34.44%
Carbamazine	17	8.133%
Lorazepam	39	18.660%
Clobazam	48	22.96%
Levetiracetam	7	3.3492%
Phenobarbital	15	7.17%
Midazolam	4	1.91%
Valproic acid	7	3.34%
Total	209	100%

Table No.5: Shows 8 different types of antiepileptic. In 120 prescriptions these drugs were prescribed 209 times. Number of drugs per prescription was 120/209 i.e. 1.74.Extent of utilization of individual drugs in descending order were phenytoin 34.44% followed by carbamazepine 8.133%, lorazepam 18.6%, clobazam 22.96%, levetiracitam 3.34%, phenobarbital 7.17%, midazolam 1.91%, valproic acid 3.34%. Following was the utilization pattern of these drugs presented in figure.

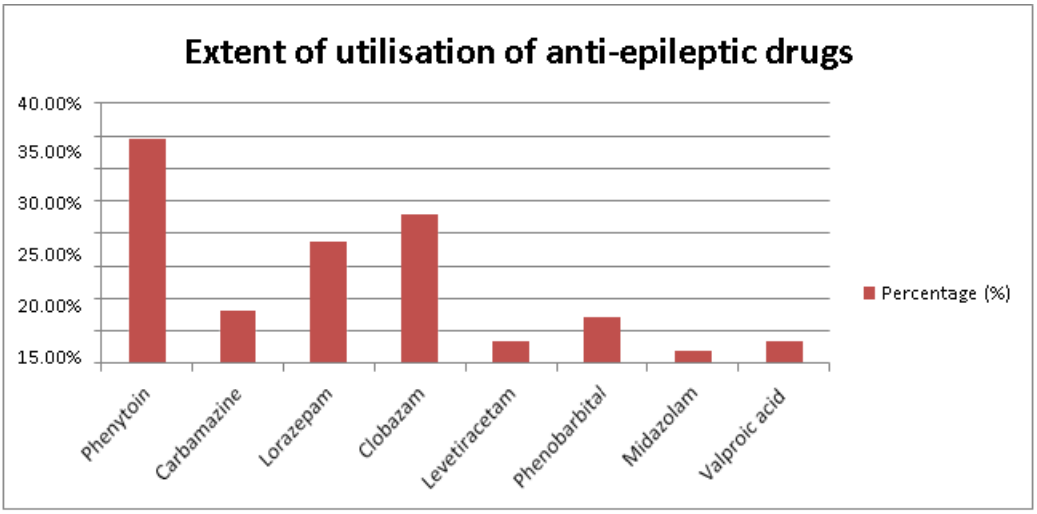

Figure No.4: Extent of utilization of individual anti-epileptics.

Table No 6: Generation of Antiepileptic Agents.

Type of antiepileptic drugs	Frequency(N)	Percentage (%)
Newer generation antiepileptics	8	3.82
Older antiepileptics	201	96.1
Total	209	100

Table No 6: Older Vs Newer generation of antiepileptics. We have seen only 1 newer generation antiepileptic agent i.e. levetiracetam which accounts for 3.82% of newer generation antiepileptics in our study. It was used always in conjuction with older antiepileptic drugs as for adjunctive therapy. Remaining 201 i.e. 96.1% of drugs were older generation and they were 7 different types as mentioned in table number 5.

Table No.7: Adverse Drug Reactions

Adr And Its Description	
Drug Name	Carbamazepine
Dose	200 mg
Frequency	Once a day
ADR	Erythema Multiforme Majus.
Age	12
Sex	Female
Naranjo Scale	Probable
Intervention	Accepted and withdrawn of drug immediately
Prevalence	1 out of 17 cases

Table No.7: Out of 120 patients, 17 were exposed to carbamazepine, we had found 1 case of carbamazepine induced erythema multiforme majus.

DRUG - Drug Interactions

Table No.8: Type of Drug Interactions.

Type of drug interaction	Frequency (N)	Percentage (%)
Mild	32	39.02
Moderate	14	17.073
Severe	36	43.902
Total	82	100

Table No.8: It showed that that in majority of prescriptions having drug interactions, drug interactions were mostly severe. i.e.36 (30%) which were followed by mild type of interaction 32 (26.66%) and moderate type of interactions14 (11.66%) respectively. Following was the graphical representation of various types of drug interactions.

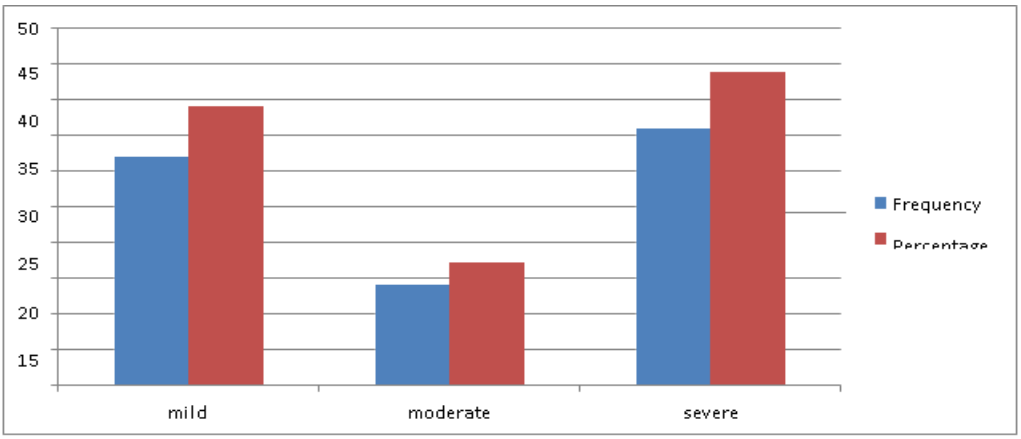

Figure No. 9: Graphical representation of different types of drug interactions.

Table No.9: List Of Drug-Drug Interactions.

Objective drug	Precipitated drug	Frequency (N)	Percentage (%)
Phenytoin	Metronidazole	2	2.439%
Phenytoin	Phenobarbital	2	2.439%
Ondansetron	Phenobarbital	4	4.878%
Phenobarbital	Lorazepam	3	3.658%
Clobazam	Phenobarbital	4	4.8780%
Albendazole	Phenytoin	3	3.658%
Acetaminophen	Metronidazole	1	1.219%
Calciumgluconate	Amikacin	3	3.65%
Calciumgluconate	Ceftriaxone	3	3.658%
Atorvastatin	Metronidazole	4	4.878%
Vancomycin	Amikacin	3	3.65%
Pantoprazole	Phenobarbital	5	6.09%
Pantoprazole	Clobazam	3	3.65%
Acetaminophen	Lorazepam	5	6.097%
Acetaminophen	Phenytoin	8	9.75%
Atorvastatin	Phenobarbital	4	4.87%
Amikacin	Phenytoin	2	2.43%
Phenytion	Valproic acid	3	3.65%
Carbazepine	Valproic acid	4	4.87%
Valproic acid	Aspirin	1	1.21%
Carbazepine	Pantaprazole	7	8.53%
Lorazepam	Clobaz	3	3.65%
Pantaprazole	Phenytion	2	2.43%

Lorazepam	Alprazolam	2	2.43%
Alprazolam	Phenobarbitone	1	1.21%
Total drug interaction		82	100%

Table No.9: It showed that out of 120 prescriptions, 82 different drug-drug interactions were identified. Most commonly (9.75%) we seen acetaminophen plus phenytoin were interacting. Other different drug interactions were as shown in table.

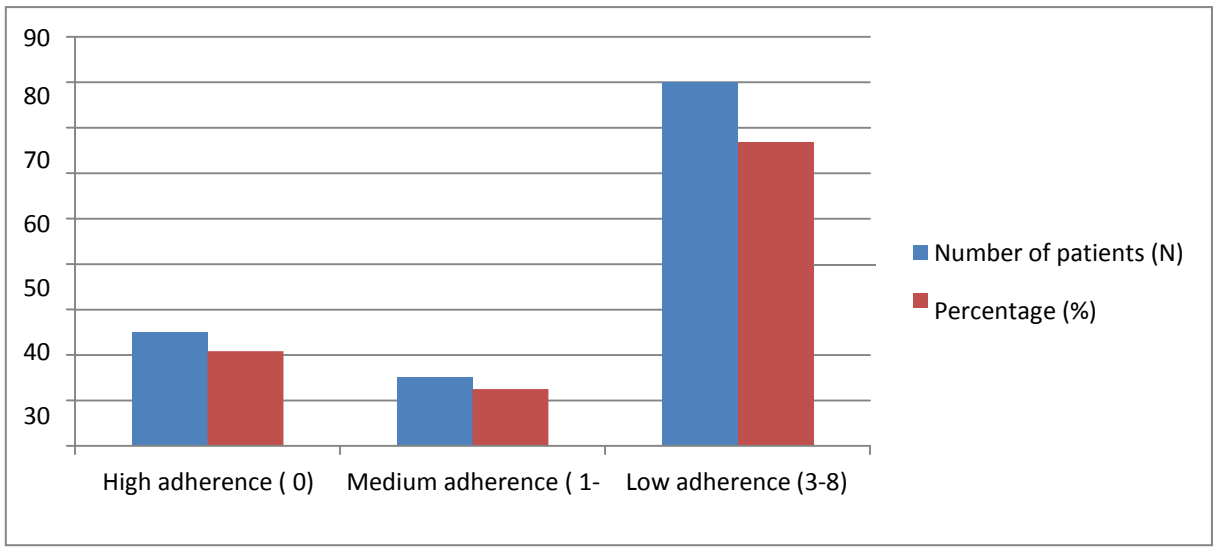

Figure No 10: Level and Score of medication adherence behavior of patients in MMAS-8Questionnaires.

Table No.10: Clinical Pharmacist Mediated Interventions In Nut Shell.

Clinical pharmacistservice provided	Drug relatedproblems	Notified to physician	Physcian Acceptance	Action taken
Identification of Drug interaction	Severe drug interaction	Yes	Yes	Monitoring of clinical effects
	Moderate drug interaction	Yes	Yes	Not taken
	Mild drug interaction	Yes	Yes	Not taken
Identificationand ADR monitoring	Reversible carbamazepineinduced rashes	Yes	Yes	Drug Withdrawn
Patient counselling	Low medication adherence level	Yes	yes	Patient counselling provided by clinical pharmacist

Table No.10: It showed that all the drug related problems either potential or actual were notified to physician where all got accepted but only in cases of severe drug interaction, low medication adherence and adverse drug reaction further action was taken.

DISCUSSION

This study provides the insights of current trend of antiepileptic drugs utilization pattern in rural tertiary care teaching hospital.

DEMOGRAPHIC DETAILS OF PATIENTS GENDER DISTRIBUTION

Among 120 patients studied; we seen female (N=70, 58.33%) were predominant than males (N=50, 41.66%). In contrast to our results; Murthy NV et al showed males were more frequently attacked with epilepsy than females.[7] It is however that T.Badwaik et al seen females were more than males in their study exposed to antiepileptic drugs, which complements our result.[48]

AGE DISTRIBUTION

In our study we frequently found more pediatric (70) cases i.e., age group less than 18 years than adults (50) cases. From medicine units most patients were between 36-60 age groups. According to the literatures, the incidence of epilepsy has a bimodal distribution with a peak in the first decade and a second peak in the elderly and our result is in accordance with it.[55, 56, 57]

DIAGNOSIS AND CO-MORBIDITIES

Most frequent diagnosis in our study was epilepsy

without any co-morbidity which accounts for 80% of diagnosis. It tells that epilepsy due to co-morbidities are less in our study. Generalized tonic clonic (GTC) seizure was the most common type of epilepsy. This result is similar to studies from Akinsulore A et al and Murthy NV et al where they also seen GTCs as a major diagnosis.[7,39] Rest of the 20% of diagnosis were associated with co-morbidities like both diabetes and hypertension, meningitis, cardiovascular accident, alcohol withdrawal syndrome, viral fever, migraine, and bronchopneumonia. Junny Sebastian et al also seen hypertension as most common comorbidity like our study,[30] but always it will not be the same case. Study from Germany found cerebrovascular accident, dementia, and intra cerebral hematoma as a most common comorbidities.[58]

TYPES OF EPILEPSY

In our hospital most patients were suffering from generalized tonic clonic seizures during this period followed by atypical seizures, typical seizures, status epilepticus, febrile seizures, partial seizures, generalized tonic clonic seizures by alchohol dependence and by hot water and febrile seizure. A study from Mysore, south India also seen similar pattern of epilepsy.[30]

DRUG UTILISATION EVALUATION OF ANTIEPILEPTIC DRUGS

There are above 20 antiepileptic drugs which are available for clinical use today. In our hospital only 8 different antiepileptic drugs were used however. In 120 prescriptions; 209 were antiepileptic drugs and 163 non antiepileptic drugs. This study highlighted that Phenytoin was the most commonly prescribed antiepileptic drug. Similar results were obtained by Sobhana et al.[58] Recently published studies (2002-2013) mention that sodium valproate was the most commonly drug prescribed followed by phenytoin or other drugs.[7,49,60,61,62] We seen very less prescription for this drug however (3.34%). An Indian study by Thomas SV et al 2001 mentioned that carbamazepine was prescribed most commonly.[63] Comming into the lesser side we had seen very less prescription for drugs like midazolam and levetiracetam. This shows the existing of wide variation of prescribing in antiepileptic drugs. The reason for discrepancies may be due to factors like availability, affordability, place of practice, type of epilepsy and preference of treating neurologist etc. Phenytoin is broad spectrum antiepileptic most commonly used for partial onset seizure as well as generalised clonic tonic seizures. As it is less expensive, it is also widely available, which enhances its use in our set up of tertiary care hospital. We also found some non-antiepileptic drugs prescribed due to different co-morbidities. Most common was non steroidal anti-inflammatory drugs followed by antibiotics, antidiabetics, H2 receptor antagonist etc. Due to these con-current drugs we found potential drug-drug interactions with antiepileptic agents. We also seen that 90 % of prescriptions were containing at least one parenteral formulation and 10 % of prescriptions were containing oral formulations. We had also seen that varying number of dosage forms in prescriptions. i.e from 1 dosage form in a prescription to 4 different dosage forms. If there are different types of dosage forms prescribed for a patient, patient counseling especially about administer technique is needed to increase compliance. For example in some cases suppositories, tablets, syrups, injections were prescribed for same patient. We witnessed the fact that majority of patient are not aware of how to administer different dosage forms.

INDICATION WISE USE OF ANTIEPILEPTIC DRUGS

Drug therapy is the mainstay of epilepsy treatment. The choice of antiepileptic drugs will depend on types of epilepsy, drug specific adverse drug reactions and patient preferences. To treat epilepsy, basic treatment approach is to begin with monotherapy where about 50% to 70% of patients can be maintained on one antiepileptic drug but all are not seizure free.

In GTCs which accounts for frequent diagnosis; phenytoin 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 1st drug introducing polytherapy. All the time phenytoin and another anti-epileptic drug combination were used as polytherapy except in one case where clobazam and midazolam was also used to treat GTC. Most commonly used add on antiepileptic was lorazepam followed by carbamazepine, phenobarbital, clobazam withphenytoin which introduced polytherapy. At maximum upto 4 different antiepileptic drugs were used to treat different GTCs. These all things highlighted the fact that to treat GTCs, still traditional approach of using phenytoin/Phenobarbital was continued. Carbamazepine and valproic acids also have equal efficacy and fewer side effects and can be preferred. dipiro. Carbamazepine is considered an AED of first choice for newly diagnosed partial seizures and for primary GTC seizures that are not considered an emergency whereas valproic acid is alsoindicated to treat mixed seizure disorders. No newer antiepileptics as adjunctive therapy was noted. We also found considerable difference in therapy to treat GTCs caused by hot water and alcohol abuse. Clobazam as a monotherapy, and lorazepam plus clobazam as polytherapy was used commonly to treat hot water GTCs. However to treat alcohol abuse related GTCs, phenytoin plus lorazepam combination was used most commonly. In typical seizure monotherapy with clobazam was preferred choice however if they required polytherapy theywere tried with Phenobarbital as adjunct to clobazam. Some cases of typical seizures were treated with combination that started with phenytoin as a monotherapy. Similarly in febrile eizures most commonly carbamazepine was used rather than phenytoin. To treat status epileptics phenytoin and its combination with other antiepileptic like lorazepam,

Phenobarbital, levetiracetam and midazolam was used. Maximum of upto 4 drugs were used. Similarly to treat partial seizures levetiracetam and carbamazepine as monotherapy was used. Focal and atypical seizure there was high use of phenytoin.

Based on these findings we highlighted that phenytoin was mostly used. Phenytoin was not used to treat febrile seizures. Carbamazepine was used in these cases. Levetiracetam was used as monotherapy as well as in combination with carbamazepine to treat focal seizures only.

Valproate was used as adjunctive therapy in different types of epilepsy including status epilepticus. Clobazam was used as monotherapy specially to treat hot water epilepsy and with different indication as polytherapy. Lorazepam alone was never used but only in combination it was used. Phenobarbital was not used in partial, atypical, focal seizures but when used it was utilized as adjunctive therapy to treat other indications. Midazolam was used in case of just GTCs and status epilepticus as adjunctive therapy.

MONOTHERAPY VS POLYTHERAPY.

Problems in polytherapy is undue increase in cost, drug interaction with other drugs, increased chance of side effects and less compliance to patient which can be complicating the therapy leading to decrease in therapeutic outcome. Careful administration of other antiepileptic isneeded if necessary.

In our study we found that 35.83% of the patients were on monotherapy and 64.16% were on polytherapy i.e. > 2 or more antiepileptic drugs. These results are not in conjuncture with other studies.[7, 59, 49, 61] where they found that most of the patients (≥50%) were prescribed single drug. Guidelines mention that medical management of newly diagnosed epileptic patients should start with monotherapy. Polytherapy should be considered when failure of two attempts of monotherapy.[65] In our study upto 4 different antiepileptic drugs were prescribed in a prescription at maximum but poly therapy by two antiepileptics were most common. This may be due to the fact of failing of monotherapy or using polytherapy by physician at once in severe or life threatening situation. Failing of monotherapy may also result from lack of adherence resulted from no proper counseling about their medication to the rural patient. It is found that up to 60% of patients with epilepsy are noncompliant, and this is the most common reason for treatment failure.[35]

UTILISATION OF NEWER VS OLDER ANTIEPILEPTICS

Drugs introduced before 1990's are called older and after 1990's are newer antiepileptic drugs. We found very less new antiepileptic drugs than older ones in prescriptions. This is similar to studies performed in India highlighted the limited use of newer anti-epileptics drugs.[49] Guidelinesfor the management of epilepsy in India, 2013 shows that newer antiepileptic drugs and their discovery has not altered treatment regimen.[64] However it has increased treatment choice in refractory cases. So far, no studies have shown that the newer drugs have superior anticonvulsant efficacy than older ones but have favorable side effects. Less use in our settings may also be due to higher cost of these agents compared to older ones. In our study we found Levetiracetam as only one newer antiepileptic and older ones include Carbamazepine, Phenytoin, Valproate, Clobazam, Lorazepam, Phenobarbital and Midazolam. Most commonly poly-therapy include two drugs per prescription other than 3 drugs per prescription and 4 drugs per prescription.

ADVERSE DRUG REACTION

A Female of 12 years of age took Carbamazepine 200 mg O.D for partial seizure and after 2 daysshe developed skin rashes all over the body. It was identified as erythema multi-form. The reaction was a Type B based on Rawlins and Thompson classification. According to Naranjo scale and WHO scale and it was probable ADRs. We notified this adverse drug reaction to attending physician. The intervention was accepted and drug was tapered before withdrawn. They added levetiracetam 10 mg once daily. Due to this adverse drug reaction patient got 1 more day of hospitalization was observed. This reaction with carbamazepine occur 1-2 every 100,000 patient population. In our study we seen this reaction out of 17 patient exposed to this drug. This reaction mimics steven johonson and toxic epidermal necrosis which can also occur by this drug. However this reaction is characterized by erythema and moderate to extensive scaling of involvement of total or near total body surface. Upto now no patient had died due to this reaction and is not severe.[65] The adverse drug reaction was reversible as rashes disappeared upon discontinuation.

DRUG INTERACTIONS

Drug interaction determines the safety aspects of drug use. Clinically it can be classified as mild, moderate and severe whereas based on the mechanism; it can be divided into pharmacokinetic and pharmacodynamic interactions.[66] We seen different antiepileptic drugs interacting with both antiepeileptic drugs and also with other drugs used for co-morbidities. As in our study majority of drugs are older generations they have high chance of interaction. In therapeutics, these classes of drugs are mostly interacting drugs.[35] Drug-drug interaction among antiepileptic drugs can happen due to refractory cases of epilepsy requiring polytherapy and use of antiepileptic drugsfor multiple indications etc,[66] in our study. The potential for interactions with other drugs increase with increasing age, and the elderly is the largest group with new onset epilepsy having a considerable risk of interactions with commonly prescribed drugs etc.[67]

TYPE AND MECHANISM OF DRUG INTERACTION

In our study we found more cases of severe type of drug interaction followed by mild and moderate cases. All these interactions were potential interactions. There are two mechanisms by which drug-drug interaction may take place. They are pharmacodynamic and pharmacokinetic mechanism. Pharmacodynamic interactions are those which occur at the drug's site of action and do not involve change in plasma drug concentrations but alter i.e attenuate or enhance efficacy and adverse effects. There was very less amount of such interaction in our setting. Most commonly we saw pharmacokinetic drug interaction. In general, pharmacokinetic interactions may alter absorption, protein binding, metabolism, and excretion of any drug, They are usually related to alterations in metabolism by enzyme inducers or inhibitors. Enzyme induction involves the synthesis of new enzyme, requires protein synthesis and may take many days before it is completed, resulting in increased metabolism, decreased serum concentrations and pharmacological effect (if no active metabolites are present) of the affected drug, and possibly loss of seizure control. Enzyme inhibition results from competition between drugs for the same active site on the enzyme and results in decreased metabolism of the affected drug. Circulating concentrations of the inhibited drug increase to a new steady-state about five half-lives after the interaction. Consequently, pharmacological potentiation will occur quickly if the drug has a shorthalf-life and more slowly if it has a long half-life (20-23). In our study we found 80% of drug interactions were pharmacokinetic, 4.87% of drug interaction were pharmacodynamic and 14% were both pharmacokinetic and pharmacokinetic. Our study highlighted that mostly drug interaction will occur through pharmacokinetic interaction.

DIFFERENT INTERACTING DRUGS

Among 82 potential drug interactions we seen 8 different interactions were having both antiepileptic drugs and rest of them (74) were having interaction with other drugs used for co- morbidities. Phenobarbital was mostly interacting with number of other drugs possibly through enzyme induction. Likewise Carbamazepine plus Pantoprazole accounted for frequently encountered drug interaction in our settings.

MEDICATION ADHERENCE BEHAVIOR OF PATIENT

Adherence to medication is defined as the extent to which a patient's behavior taking the medication prescribed by the physician changes after therapeutic plan agreement is established between patient and physician.[72] Adherence level of patient will focus on patient's drug related problems which can be resolved. In epilepsy patient they have to take medications for years. So to observe medication adherence behavior to this patient useful. Medication adherence can be assessed by either indirect or direct methods. Direct methods to measure adherence are attendance to direct observed therapy and measurement of the level of medication or metabolite and biological markers in the blood.[72] Indirect methods include patient self-reporting, records of drug refills, pill counts, patient's treatment response assessment and the use of electronic medication-monitoring devices. We used patient self reporting indirect method to assess medication adherence by validated MMAS-8 questionnaires. This questionnaire consist 8 questions where 0 is given to answer 'Yes' and 1 is given to answer 'No' from question 1 to 7 where as in question number 8, answer are reported in 0 to 4 scale. After filling the questionnaire one can add all the score to provide medication adherence score for patient which can come from 0 to 8.Further these score are classified as adherence level as high adherence(0), medium adherence(1-2) and low adherence(3-8).

The prevalence of self-reported poor adherence to AED therapy among our study subjects is poor and is contrast to those reported in previous studies of the western population.[72] Very high level of non adherence has also been reported from Malaysia.[74] In 2003, WHO reported that the prevalence of adherence to AEDs in developing countries ranged between 20% and 80%. 26 Hence, our finding showed that the issue of poor adherence is not changing in India. As we found 66.66% of patient were having low adherence and 12.5% of patient were having medium level of adherence. These were the poor adherence groups. So we counseled them to improve further of their medication adherence behavior. Base line follow up to see the outcome however was not done.

These patient who were having poor adherence, may had multiple reason for this.[72] In younger age patients; medication taking behavior will depend on their care takers. Care takers and patient themselves are will not be aware to seek proper medication advice. Poor understanding about the nature of, and need for the AED therapy could lead to poor adherence level. In these instances patients will realize the benefits of adherence only as time passed because they learn from their personal experience.[73] WHO also reported that patients with busy lifestyles commonly do not adhere to medication.[75] but this was the common reason in our settings. Very interestingly one study reported that more than half of the epilepsy patients thought that they could reduce or cease taking the AEDs just to see what would happen.[76]

CLINICAL PHARMACIST MEDIATED INTERVENTIONS IN NUT SHELL

Drug related problems can be potential and actual. Potential are those which will happen in near future but actual drug related problem are those which was already happened. All drug interactions in our study were potential. ADR and low adherence level were actual drug related problems. These problems were all notified to the respective physician. They accepted all these problems but only in cases like ADR and severe drug

interaction further action were taken. Drug was withdrawn immediately in case of ADR but in case of some drug interactions they monitor clinical effect. In all patients having low to moderate adherence level we counseled the patient regarding disease and medication. We highlighted the role of clinical pharmacist in this research work by identifying and resolving drug related problems. We want to conclude that physician acceptance of clinical pharmacist role is increasing in our hospital.

CONCLUSION

Based on the results we would like to conclude that- Prescribing pattern of antiepileptic drugs shown very less prescriptions for newer antiepileptic drugs. Only one drug i.e. Levetiracetam was used. Newer antiepileptic drugs can be tried in practice as indicated because they have less side effects. Most commonly phenytoin was utilized. This is enzyme inducing drug and will show non-linear pharmacokinetics. So Therapeutic drug monitoring is essential.Poly therapy in prescriptions is more than monotherapy and majority of patients were having low medication adherence. Patient counselling service is needed which can improve the patient medication taking behavior.

Because of co-morbidities; antiepileptic drugs have more chance of interaction with other drugs. So before prescribing other drugs we have to check this drug interaction. Clinical pharmacist mediated drug interaction monitoring service will be useful in this regard. Because ADR incidence of antiepileptic drug is high, ADR identification and reporting has to be encouraged to nurses, physician and even to the patients.

REFRENCES

1. Shelat PR, Gandhi AM and Patel PP. A study of drug utilization pattern according to daily define dose in intensive care unit (ICUs) at tertiary care teaching hospital. Indian J of Young Pharmacists, 2015; 7(4): 344-58.
2. Sjoqvist F and Birkett D. Introduction to drug utilization research. Chapter, 10. 2003; 78-84.
3. Chowdhury D. New drugs for the treatment of epilepsy: a practical approach. Supplement to Journal of the Association of Physicians of India, 2013; 61: 19-39.
4. Mane YV, Potey A, Bhide SS, Jalgaonkar SV and Ravat SH. Drug utilization pattern of antiepileptic drugs and direct and indirect cost estimation in the treatment of epilepsy at tertiary care hospital. Int J Information Res & Review, 2015; 2(6): 759-64.
5. Vettikkadan AR, Jith A, Krishnaveni K and Kumar SR. Study of utilization pattern and drug interactions of anti-epileptic drugs in a private hospital. Asian J Pharm Clin Res, 2014; 7(5): 164-66.
6. Patsalos PN. Anti-epileptic drug interactions. A Clinical Guide. Springer, 2013.
7. Murthy VN, Anusha B and Perumal P. A Study on trends in prescribing pattern of anti- epileptic drugs in tertiary care teaching hospital. Int J of Chemical & Pharma Sci, 2012; 3(2): 25-32.
8. Mazhar F, Shamim S and Malhi SM. Drug utilization evaluation of antiepileptics in three selected multidisciplinary teaching hospitals of Pakistan. Int J Pharmacy & Pharma Sci, 2014; 6(5): 59-66.
9. Purcell B. Epilepsy prevalence and prescribing patterns in England and Wales. Health Statistics Quarterly, 2002; 15: 23-30.
10. Loscher W and Potschka H. Role of multidrug transporters in pharmacoresistance to antiepileptic drugs. The J Pharmacology & Experimental Therapeutics, 2002; 301: 7-14.
11. Johannessen SI and Johannessen C. Antiepileptic Drug interactions - principles and clinical implications. Current Neuropharmacology, 2010; 8: 254-67.
12. Aneja S and Sharma S. Newer anti-epileptic drugs. Indian Pediatrics, 2013; 50(15): 1033-40.
13. Coata E, Giardini A, Savin M, Menditto E, Lehane E and Laosa O. Interventional tools to improve medication adherence. Patient Preference and Adherence, 2015; 9: 1303- 1314.
14. Ahmad N, Othaman NI and Islahudin F. Medication adherence and quality of life in epilepsy patients. Int J Pharm Sci, 2013; 5(2): 401-404.
15. Stefan H. Improving the effectiveness of drugs in epilepsy through concordance. ACNR, 2009; 8(6).
16. Zhao BMS, Eric C, Wong MS and Palaniappan L. Estimating patient adherence to medication with electronic health records data and pharmacy claims combined. Sas Global Formula, 2013: 1-7.
17. Chadwick D and Reynolds EH. When do epileptic patients need treatment starting and stopping medication. Br Med J (Clin Res Ed), 1985; 290: 1885-88.
18. Anderson M, Egunsola O, Cherrill J, Millward C, Fakis A and Choonara I. Prospective study of adverse drug reactions to antiepileptic drugs in children. BMJ, 2015; 5: 1-7.
19. Schlienger RG, Oh PI, Knowles SR and Shear NH. Quantifying the costs of serious adverse drug reactions to antiepileptic drugs. Epilepsia, 1998; 39(7): 27-32.
20. Ramakrishna P and Ramaiah M. Collection, detection, assessment, monitoring and prevention of adverse drug reaction of antiepilepticus. Int Res J Pharma, 2014; 5(8): 653-57.
21. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmaco, 2005; 61: 3246-55.
22. Brijal PS, Amita KR, Divyesh SB and Piparva. Drug utilization study in neonatal intensive care unit at tertiary care hospital, Rajkot, Gujarat: A prospective study. World J of pharmacy & Pharmaceutical Sci, 2015; 4(7): 2034-42.
23. Jena M, Jena SS and Dash M. Monitoring of prescriptions and pharmacovigilance evaluation of

antiepileptic drugs in a tertiary care teaching hospital. Int J Pharm Sci. Rev. Res, 2014; 29(1): 99-104.
24. Jyothi K and Babu JD. Drug utilisation evaluation of cephalosporin's in general medicine units of rural tertiary care hospital. Int J Current Pharma Res, 2012; 4(2): 88- 91.
25. Sachdeva PD and Patel BG. Drug utilization studies- scope and future perspectives. Int J on Pharma & Biological Res 2010; 1(1): 11-17.
26. Available from: www.amcp.org.
27. Parthasarathi G. Textbook of Clinical Pharmacy Practice. 3rd edition. Page 362-72.
28. Lowenstein DH. Seizures and Epilepsy. Diseases of the central nervous system. Harrison's Principles of Internal Medicine. 16th ed. 2361.
29. Miriam N. Non adherence to antiepileptic drugs in a child with epilepsy: A case report. Int Invention J Medicine & Med Sci, 2015; 2(2): 29-33.
30. Sebasteian J, Adepu R, Keshava BS and Harsha S. Assessment of antiepileptic drugs usage in south indian tertiary care teaching hospital. Neurology Asia, 2013; 18(2): 159- 65.
31. Shaik R, Akhil A, Rani S, Hiremath R and Usha HN. Study of anti-epileptic therapy in pediatric patients in a secondary care hospital. World J of Pharmacy & Pharma Sci, 2015; 4(11): 2052-62.
32. Friedman JN. Emergency management of the pediatric patient with generalized convulsive status epilepticus. Pediatric Child Health, 2011; 16(2): 917.
33. Marvin M. Overview of drugs used for epilepsy and Seizures. P&T®, 2010; 35(7): 392- 14.
34. Gidal BE and Garnett WR. Epilepsy pharmacotherapy: A Pathophysiologic Approach. Sixth edition. Dipiro JT, Talbert R and Yee GC and Wells BG, 2005; 1023.
35. Wells BG, Dipiro JT, Schwinghammer T and Dipiro CV. Pharmacotherapy hand book seventh edition. Page 577.
36. Martindale. The Complete Drug Reference. Thirty-sixth edition, 2009.
37. Harrison R, Daniel H and Lowenstein. Harrison's Principles of Internal Medicine. 16th edition. Page 2357.
38. www.patient.co.uk/doctor/anticonvulsants-used-for-generalised seizures.htm.
39. Akinsulore A and Adewuya A. Psychosocial aspects of epilepsy in Nigeria. African J of Psychiatry, 2010; 13: 351-56.
40. Sidig A, Ibrahim G and Hussein A. A Study of knowledge, attitude, practice towards epilepsy among relative of epileptic patients in Khartoum state. Sudanese J of Public Health, 2009; 9(9): 393-98.
41. Lakshmi C, Babitha, Ramesh, Dhanapal and Manavalan. Role of clinical pharmacist in rational therapy of pediatric seizures. Int Current Pharma J, 2012; 1(10): 328-31.
42. Elberry AA, Felemban RK, Hareeri RH and Kurdi SM. Efficacy and safety of levetiracetam in pediatric epilepsy. Saudi Pharma J, 2012; 20: 81-84.
43. Britton JW and Shih JJ. Antiepileptic drugs and suiciability. Drug Healthcare and Patient Safety 2010; 2: 181-89.
44. Daniel F, Connor, Kaan R, Ozobayrak, Robert J, Harrison and Melloni RH. Prevalence and patterns of psychotropic and anticonvulsant medication use in children and adolescents referred to residential treatment. J of Child and Adolescent Psychopharmacology, 1998; 8(1): 27-38.
45. Sanjeev V T, Samuel and Sudhakaran Nair CR. Frequent seizures and polytherapy can impairment quality of life in persons with epilepsy. Neurology India, 2005; 53(1): 46- 50.
46. Rana PVS. Managing epilepsy: medical management. Nepal Journal of Neuroscience, 2004; 1: 73-82.
47. Chalapathi Rao KN, Siddnathi Narasinga Rao, Atluri Sridevi and Naga Pavankumar. Clinical and radiological evaluation of new-onset epileptic seizures in a tertiary care hospital. Evidence Based Med & Healthcare, 2015; 2(39): 6452-57.
48. Badwaik TR, Mahajan MH, Borker SA, Honrao R and Chopade SS. A drug utilization study of antiepileptic drugs use in a tertiary care hospital of central India. J Cont Med a Dent, 2015; 3(2): 33-38.
49. Arulkumaran KSG, Palaniswamy S and Rajasekaran A. A study on drug use evaluation of anti-epileptics at a multispecialty tertiary care teaching hospital. Int J Pharmtech Res, 1(4): 1541-47.
50. Viswanathan S. Drug utilization study of anti-epileptic drugs in pediatric population. J Neurol Neurophysiol, 2014; 5(5): 58-64.
51. Maity N and Gangadhar N. Trends in utilization of antiepileptic drugs among pediatric patients in a tertiary care hospital. Current Neurobiology, 2011; 2(2): 117-23.
52. Getachew H, Dekemanh, Awo SS, Abdi AA and Mohammed. A medication adherence in epilepsy and potentional risk factors associated with non adherence in tertiary care teaching hospital in Southwest. Ethiopia Gaziantep Med J, 2014; 20(1): 59-65.
53. Rishel W, Seiful MF, Gelawa BK and Gunasekaran T. Drug use Evaluation of Antiepileptic Drugs in Outpatient Epilepsy Clinic of Bishoft General Hospital, East Shoa, Ethiopia, 2015; 4(3): 1516-1528.
54. Waleed S, Manal S, Ihbesheh, Jarar IS and Taha AM. Self-reported medication adherence and treatment satisfaction in patients with epilepsy. Epilepsy & Behavior, 2011; 21: 301-05.
55. Caprio A and Hauser WA. Epilepsy in the developing world. Curr Neurol Sci Rep, 2009; 9(4): 319-26.
56. Hanssen Y, Dulue D, Al Balushi K, Al Hashar A and Al Zakwani I. Drug utilization pattern of anti-epileptic drugs: a pharmacoepidemiologic study in

Oman. Journal of Clinical Pharmacy and Therapeutics, 2002; 27: 357-64.
57. Lim SH and Tan EK. Pattern of antiepileptic drug usage in a tertiary referral hospital in Singapore. Neurol J Southeast Asia, 1997; 2: 77-85.
58. Shackleton DP, Westendorp RG, Trenite DG and Vandenbrouke JP. Mortality in patients with epilepsy: 40 years of follow up in a dutch cohort study. J Neurol Neurosurg Psychiatry, 1999; 66: 630-40.
59. Shobhana M, Sumana S, Ramesh L and Satish Kumar M. Utilization pattern of antiepileptic drugs and their adverse effects, in a teaching hospital. Asian Journal of Pharmaceutical and Clinical Research 2010, 3(1); 55-59.
60. Pathak S, Singh L, Singh T and Sharma SK. Prescribing patterns of anti-epileptic drug in different age group in India. IJPPS, 2013; 1(7): 69-75.
61. Malerba A. et al. Patterns of prescription of antiepileptic drugs in patients with refractory epilepsy at tertiary referral centres in Italy, 2011.
62. Landmark CJ, Fossmark H, Larsson PG, Rytter E and Johannessen SI. Prescription patterns of antiepileptic drugs in patients with epilepsy in a nationwide population. Epilepsy Res, 2011; 95(1-2): 51-9.
63. Thomas SV, Sarma PS, Alexander M. et al. Economic burden of epilepsy in India. Epilepsia, 2001; 42: 1052-60.
64. Guidelines for the management of epilepsy in India. Indian epilepsy society 2008. [accessed 18th october 2013]
65. Akhyani M, Ghodsi ZS and Toosi S, Daabghian H. Erythroderma : A clinical study 97 cases. BMC Dermatol, 2005; 5:5: 51-58.
66. Johannessen Landmark C, Larsson PG, Rytter E and Johannessen SI. Antiepileptic drugs in epilepsy and other disorders: A population-based study of prescriptions. Epilepsy Res, 2009; 87: 31-39.
67. Levy RH and Collins C. Risk and predictability of drug interactions in the elderly. Int. Rev. Neurobiol, 2007; 81: 235-51.
68. Kim RB. Drugs as p-glycoprotein substrates, inhibitors and inducers. Drug Metab Rev, 2002; 34: 47–54.
69. Ynold TW, Dussault I and Forman BM. The orphan nuclear receptor SXR coordinatively regulates drug metabolism and efflux. Nat Med, 2001; 7: 584–90.
70. Giessmann T, May K, Modess C, Wegner D, Hecker U, et. al. Carbamazepine regulates intestinal P-glycoprotein and multidrug resistance protein MRP2 and influences disposition of talinolol in humans. Clin Pharmacol Ther, 2004; 76: 192–200.
71. Perucca E, Hebdige S, Frigo GM, Gatti G, Lecchini S, Crema A. Interaction between phenytoin and valproic acid: plasma protein binding and metabolic effects. Clin Pharmacol Ther, 1980; 28: 779–89.
72. Osterberg L and Blaschke T. Adherence to medication. N Engl J Med, 2005; 353: 487- 97.
73. Sweileh WM, Ihbesheh MS, Jarar IS, et. al. Selfreported medication adherence and treatment satisfaction in patients with epilepsy. Epilepsy Behav, 2011; 21: 301-5.
74. Tan, Makmor-Bakry, Lau, Tajarudin, Raymon. Factors affecting adherence to antiepileptic drugs therapy in Malaysia, Neurology Asia, 2015; 20(3): 235-41.
75. WHO. Adherence to Long-term therapies: Evidence for action. Geneva: World Health Organization. 2003.
76. Gomes MDM, Maia Filho HDS. Medication-taking behavior and drug self regulation in people with epilepsy. Arq Neuropsiquiatr, 1998; 56: 714-9.