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A STUDY OF DRUG UTILISATION PATTERN AND MEDICATION ADHERENCE OF ANTI EPILEPTIC DRUGS IN TERTIARY CARE HOSPITAL

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ABSTRACT

Objectives: The primary objective was to study the drug utlisation pattern of anti epileptic drugs in a tertiary care hospital. The secondary objectives of the study were to identify the common classes of drugs prescribed and indications for the therapy, to assess and identify the potential drug interactions, to identify the extent of polytherpy with antiepiletic drugd in enrolled patients, to study the medication adherence behavior among enrolled patients. **Materials & Methods:** A Prospective Observational study of 6 months duration from March 2022 to August 2022 was carried out after Institutional Ethical Committee approval. All in-patients prescribed with anti-epileptic drugs in the pediatric, general medicine and nephrology departments were selected. **Result:** A total of 150 patients were enrolled in the study and 253 antiepileptic drugs were prescribed. Male patients were more than female and the majority was in the age of 36-60 years.Generalised tonic-clonic epilepsy was the most common type followed by unclassified seizures. The most commonly prescribed drugs were phenytoin, Levetiracetam and Sodium Valproate. A lesser number of newer antiepileptic agents were used compared to older ones. The prevalence of monotherapy is high compared to dual therapy and polytherapy. **Conclusion:** The most commonly prerscibed antiepilptic drug is Phenytoin, followed by Levetiracetam. There was under utilisation of newer antiepilptics.The rate of adherence observed in this study was low, which highlights the pervasive and problematic degree of antiepileptic medication adherence. Polypharmacy can predispose to drug interactions, which result in the failure of drug therapy and an increase in the length of hospital stays.

KEYWORDS: Antiepileptic drug, Drug utilisation pattern, Drug utilisation Review, Polytherapy, Drug interaction, Medication adherence.

INTRODUCTION

Epilepsy suggest a periodic recurrence of seizures, either with or without convulsions. An Electroencephalogram (EEG) recording of a seizure shows variations in electrical activity that is caused by an excessive discharge of cortical neurons. Aconvulsion is characterized by abrupt, forceful contractions of the voluntary muscles.[1] The signs or symptoms, which might include convulsions, unconsciousness, blank staring, lip-smacking or jerking movements of the arms and legs, are sometimes missed by patients and health care professionals. A seizure has a distinct start, middle and end.[2]

Epidemiology

In India, the prevalence of active epilepsy is between 4 and 5 per 1000 people world wide. Epilepsy prevalence rates range from 4.15 to 7.03 per 1000 people. 60% of newly identified patients have partial seizures, while 40% have generalised seizures.[3]

Etiology

In about 70% of patients, there is no known reason.

1. Children who are otherwise healthy, have a structural impairment, or have genetic risk factors of seizures may experience seizures brought on by a high fever.
2. A severe, penetrating head injury or trauma is linked to a nearly 50% increased risk of developing epilepsy later on.
3. Defective synaptic activity may result in seizzures in elderly adults with alzheimer's disease, stroke, and other conditions that might trigger epilepsy.

A focus lesion of the brain appears to be the primary cause of the majority of partil epilepsy case, with a

smaller number of cases being determined by heredtary factors. For both adults and adolescents, epilepsy is frequently brought on by head trauma. Nearly 50% of occurences of epilepsy in persons over 65 are brought on by cerebrovascular illness.[4] Seizures can occur at any age as a result of metabolic abnormalities such as electrolyte imbalance, hypoglycemia or hyperglycemia, endocrine disorders, hematological disorders, renal failure and hepatic failure.[5]

Conditions most likely to stimulate a seizure are syncope and transient ischemic attacks, other possible conditions include unexplained falls ("Drop attacks"), subarachanoid hemorrhages sleep disorders (Sleepwalking, rapid-eye-movement sleep behavior disorder), panic attacks, migraine, hypoglycemia, cataplexy, paroxysmal ataxia and choreoathetosis, recurrent transient global amnesia, and psychogenic pseudo seizures.

Management

In some patients, pharmacotherapy alternatives or adjuncts may be beneficial. In certain patients, surgery is a very effective form of treatment.[4] Children seem to benefit from ketogenic diets the most; they are also used as a supplement to ongoing AED treatment.[6,7] an implantable device known as a vague nerve stimulator is approved for the treatment of uncontrollable partial seizures.[1]

Pharmacological treatment

Drugs used currently not only fail to control seizure activity in some patients, but frequently cause unwanted effects that range in severity from minimal impairment of the central nervous system (CNS) to death from aplastic anemia or hepatic failure. To minimize toxicity, treatment with a single drug is preferred. Seizures are not controlled with the initial agent at adequate plasma concentrations; substitution of a second drug is preferred to concurrent administration of a second agent. However, multiple-drug therapy may be needed, especially when two or more types of seizures occur in the same patient.[8]

Choice of antiepileptic in children: Children may be more vulnerable to some negative effects, such as those on behavior, cognition, and development; behavioral issues have been specifically linked to Phenobarbital.[9] the ketogenic diet is one dietary modification option.[10]

Benzodiazepines are the preferred first-line medication for the treatment of CSE. Seizures can be terminated with a high percentage of 70% to 85% if done so within the first 20 minutes of the onset of the episode. It is best to get IV access as soon as possible because IV administration has a quicker onset of action and improved bioavailability and efficacy.

In hospital: IV Lorazepam is usually the first-line treatment. It has a longer-lasting Anticonvulsant activity and causes less respiratory depression than diazepam.[2] it has been proven to be more successful at preventing seizures than Phenytoin or Diazepam.[11] In Second-line treatment, Fosphenytoin/Phenytoin is generally preferred over Phenobarbital because it is less likely to cause respiratory depression and alter the level of consciousness of the child, which can complicate the assessment.

Generalized Tonic-Clonic seizures: Sodium valproate is the recommended first-line medication. If Sodium Valproate is not appropriate, suggest Lamotrigine.[6]

Absence seizures: Ethosuximide or Sodium valproate as first-line treatment to children, young people and adults with absence seizures.

Myoclonic seizures: first-line therapy Provide Sodium valproate as the initial course of treatment unless otherwise indicated. If Sodium valproate is inappropriate or not tolerated, take into account Levetiracetam or Topiramate. Topiramate has a less favorable side-effect profile than Levetiracetam and sodium valproate.[7]

Treatment of women with epilepsy

Female patients with epilepsy require particular care in their treatment because female hormones (Such as estrogen and progesterone), which affect neuronal excitability, can change seizure frequency. Cataminal epilepsy is a particular issue for females. AEDs cause specific issues in them, such as changes in reproductive hormones that result in an ovulatory cycle, infertility and polycystic ovarian syndrome, worsening of osteoporosis in elderly females by adversely affecting bone metabolism, potential teratogenicity, and effects on the newborn as they cross into breast milk.

Treatment of epilepsy in geriatrics

The sedative effects of Phenobarbitone and Primidone, as well as the negative effects on cognition and mood to which this population is more susceptible, should prevent their use in elderly patients. Due to their side effects, Felbamate (hepatic toxicity and aplastic anemia) and Vigabatrin (optic neuritis) are two newer AEDs that should be avoided. The following medications are appropriate for use in elderly epileptics: Carbamazepine (with dose adjustment due to altered protein binding and altered hepatic metabolism), gabapentin (no drug interaction, but dose is adjusted to renal functions), Levetiracetam (no metabolism in liver, less protein bound, i.e. 10%, lack of drug interaction, but dose to be adjusted to renal function. Phenytoin, Carbamazepine, and Valproate dosages should be decreased due to altered pharmacokinetics (i.e., altered protein binding & hepatic metabolism). When using medications with a brief half-life, such as Carbamazepine, the frequency of administration should also be decreased.

Status epilepticus: A Benzodiazepine is typically used as the first antiepileptic medication. Although

intravenous Lorazepam is now preferred for first-line treatment in most protocols instead of the once-common Diazepam, because it appears to be more effective and has a longer duration of antiepileptic action. When intravenous access is not possible or when treating patients at home, rectal Diazepam or buccal Midazolam may be used. Although there is some evidence that Phenobarbital is more effective than Phenytoin at abolishing seizures, due to the risk of severe respiratory depression, many favor the use of barbiturate only in patients who do not respond to Phenytoin or Fosphenytoin. Patients receiving intravenous phenytoin or Fosphenytoin must have their ECGs monitored.

Febrile convulsions: Febrile convulsions are not thought to be a type of epilepsy and typically happen during the rising phase of fever early in the course of the infection that happens between the ages of 6 months and 5 years and are accompanied by a fever brought on by an infection that doesn't affect the central nervous system (CNS). Antiepileptics should not be used as a preventative measure in children who are thought to be at risk of developing febrile convulsions again.[6]

Drug Use Evaluation (DUE) / Drug Utilization Review (DUR)

DUR is an ongoing, systematic process which stands to maintain the appropriate and effective use of medications. Before, during, and after dispensing, a patient's medication and medical history are thoroughly reviewed in an effort to make the best possible therapeutic decisions and produce favorable patient outcomes.[12]

Medication adherence

The degree to which a patient follows the recommendations made regarding their health in terms of taking their medications is known as medication adherence. Medication adherence is one of the most important factors that determine therapeutic outcome, particularly in patients suffering from chronic illness. Adherence to medication is the key link between treatment and outcome in medical care.[13]

MATERIALS AND METHODS

Study design: Prospective Drug Utilization Evaluation study

Study site: The present study was conducted in medicine, nephrology and pediatrics departments of tertiary care teaching hospital (KIMS HUBLI).

Study period: The study will be conducted for a period of six months.

Study sample size: A total of 150 patients from general medicine, paediatrics, nephrology departments of KIMS, Hubli who satisfied the study criteria and consented to participate in the study were included.

Study criteria

1. Inclusion criteria

- In-patients of both sex prescribed with anti-epileptic drug in General medicine, paediatrics nephrology departments of KIMS.
- In-patients who are willing to participate in the study.

2. Exclusion criteria

- Pregnant/lactating women.
- Psychiatry patients
- ICU patients
- Patients who are not willing to participate in the study.

Sources of data

- Patient consent form
- Patient data collection form
- Patient case note/prescription
- Lab reports
- Morisky medication adherence scale questionnaire.

Study procedure

Data collection are performed using charts of every epileptic inpatient enrolled in the study for assessing drug utilization pattern and medication adherence after obtaining their written consent from patient/patient care taker. A suitably designed data collection form were used to record all the necessary data including demographic details, patient medication history, reasons for admission, medication details and lab investigations. Case note prescriptions were collected to observe the drugs used and an 8 item questionnaire is prepared & according to questions, scores will be recorded by using Morisky Medication Adherence Scale (MMAS). The MICROMEDEX database were used to evaluate patient medication regimen for potential drug- drug interactions. Drug interactions will also be categorized according to different parameters such as severity (minor, moderate, major), time of onset (rapid, delayed).

RESULTS

Patient demographics

Among 150 patients prescriptions, 96(64%) were male and 54 (48.66%) were female. The mean age of the study population were under the age group of 36-60 years (24%) in that 24 (66.66%) were male and 12 (33.33%) were female, followed by toddler 1-3 years (17%). Out of 150 patients who were recruited, 58 (38.67%) had no formal education, out of which 38 (65.51%) were males and 20 (34.49%) were females.

Distribution based on etiology

Out of 10 etiological conditions, neurological disorders (35, 23.33%) were the highest, followed by fever (31, 20.66%), poor drug compliance (28, 18.67%), CVA/stroke and syncopal attack (21, 14%).

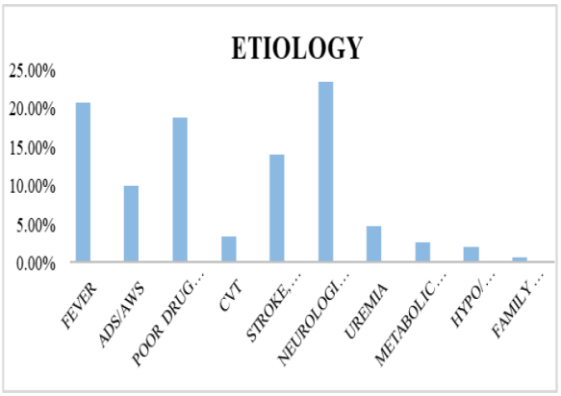

Fig. 1: Distribution based on etiology.

Distribution based on comorbidities

Out of 150 patients, 49 (32.67%) had epilepsy without any comorbid conditions, and 67.33% had comorbidities. Out of 16 comorbid conditions, neurological disorders were the most common, followed by hypertension. 15(14.85%), CVA/stroke 13(12.87%), RTI 10(9.9%), T2DM, HTN, AKI, UTI 9(8.91%).

Table 1: Distribution based on comorbidities.

Comorbidities	Frequency (N)	Percentage
1. Epilepsy Without Co-Morbidity	49	32.67%
2. Epilepsy with comorbidities	15	67.33%
a. HTN	9	14.85%
b. T2DM, HTN, AKI, UTI	8	8.91%
c. T2DM, HTN, Stroke	13	7.92%
d. CVA/Stroke	6	12.87%
e. HTN, CKD	3	5.94%
f. Urinary tract infection	4	2.97%
g. CVT	3	3.96%
h. Failure to thrive & Moderate acute malnutrition	1	2.97%
i. Gastroenteritis	1	0.99%
j. Jaundice	10	0.99%
k. RTI	1	9.9%
l. Infantile Dengue Fever	1	0.99%
m. Cervix Carcinoma	24	0.99%
n. Neurological disorders	1	23.76%
o. ADS/AWS	1	0.99%
p. Old PRES	TOTAL=101	0.99%
TOTAL	150	100%

Distribution based on types of epilepsy

GTCS (55.33%) type is higher than the other categories, which are partial seizures (2%) febrile seizures (16.66%), status epilepticus (7.33%), and unclassified seizures (18.66%).

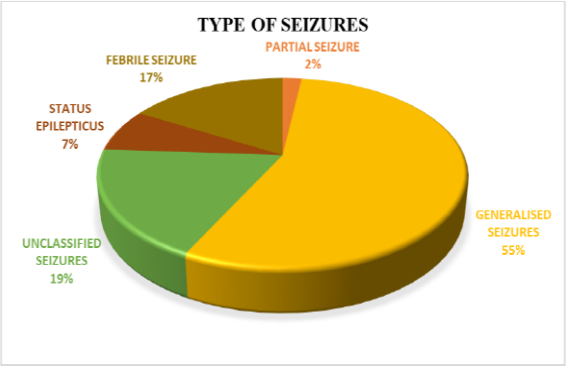

Fig. 2: Distribution based on type of epilepsy.

Distribution of epilepsy

As tabulated in Table 2; 3 of the 150 patients as 67% of the partial seizure were simple partial seizure, and 33% were complex partial seizure.

We found that 83 of the participants in our study experienced generalized seizures. In that, tonic-clonic GTCS type was seen in the majority of patients (92%), followed by tonic seizures (4%). In unclassified seizures, scar epilepsy is more common, followed by uremic seizures, GTCS by ADS/AWS, etc.

Table 2: Distribution of epilepsy.

Sl. No.	Types	Frequency	Percentage
1	Partial seizures a. Simple partial seizures b. Complex partial seizures	 2 1 Total 3	 2%
2	Generalised seizures a. Absence b. Myoclonic c. Clonic d. Tonic e. Tonic-Clonic f. Atonic g. Infantile spasms	 1 2 1 3 76 0 0 Total 83	 55.33%
3	Unclassified seizures a. Uremic seizures b. Hypoglycaemic seizures c. Hyperglycaemic seizures d. Metabolic seizures e. Scar epilepsy f. Refractory seizures g. GTCS by alcohol dependence and withdrawal h. Grand mal	 7 1 1 1 9 1 7 1 Total 28	 18.66%
4	Status Epilepticus	11	7.33%
5	Febrile seizures	25	16.66%
	Total	150	100%

Utilisation pattern of drugs

This table depicts the use of antiepileptic drugs by indication. Polytherapy was always used with phenytoin and another anti-epileptic drug combination. Up to four different antiepileptic drugs were used to treat different indications.

Table 3: Utilisation pattern of drugs.

Indication		Utilisation pattern of antiepileptics	Frequency
Partial seizure	Simple partial	Levetiracetam+phenytoin+sodium valproate	1
		Levetiracetam+lorazepam+sodium valproate	1
	Complex partial	Phenytoin	1
		Total	3
Generalised seizures	Absence seizure	Carbamazepine+ sodium valproate	1
	Myoclonic seizure	Sodium valproate	1
		Sodium valproate+ Phenytoin+ lorazepam+ clobazam	1
	Clonic seizure	Levetiracetam sodium valproate+ lamotrigine clobazam	1
	Tonic seizure	Levetiracetam	2
		Sodium valproate phenobarbital	1
	Tonic clonic seizure	Phenytoin	1
		Levetiracetam+ phenobarbital	1
		Levetiracetam	13
		Sodium valproate	7
		Phenytoin	14
		Lorazepam	1

		Clobazam	2
		Phenobarbital	1
		Phenobarbital+ clobazam	1
		Phenobarbital+ levetiracetam	5
		Phenobarbital+ phenytoin	1
		Phenobarbital+sodium valproate	1
		Phenobarbital+lorazepam	1
		Sodium valproate+clobazam	1
		Sodium valproate+lorazepam	2
		Sodium valproate+levetiracetam	1
		Sodium valproate+phenytoin	1
		Phenytoin+clobazam	1
		Phenytoin+carbamazepine	2
		Phenytoin+lorazepam	5
		Phenytoin+leveteracetam	7
		Levetiracetam+lorazepam	1
		Phenytoin+levetiracetam+lorazepam	1
		Phenytoin+sodium valproate+lorazepam	1
		Phenytoin+phenobarbital+clobazam	1
		Phenytoin+levetiracetam+sodium valproate	1
		Sodium valproate+levetiracetam+clobazam	1
		Phenytoin+sodiumvalproate+levetiracetam +phenobarbital	1
		Total	83
Unclassified seizures	Uremic seizure	Phenytoin	1
		Levetiracetam	2
		Sodium valproate+ levetiracetam	1
		Phenytoin+lorazepam	1
		Levetiracetam+carbamazepine	1
		Phenytoin+levetiracetam	1
	Hyperglycemic seizure	Phenytoin	1
	Hypoglycaemic seizure	Sodium valproate	1
	Metabolic convulsion	Sodium valproate	1
	Scar epilepsy	Levetiracetam+sodium valproate	2
		Phenytoin	1
		Levetiracetam	1
		Phenytoin+sodioum valproate	1
		Phenytoin+levetiracetam	1
		Phenytoin+lorazepam	1
		Phenytoin+sodium valproate+clobazam	1
		Sodium valproate+Levetiracetam +phenytoin	1
	Refractory seizure	Phenobarbital+clobazam	1
	Adw with aws seizure	Phenytoin +lorazepam	6
		Phenytoin	1
	Grandmal seizure	Phenytoin +levetiracetam	1
		Total	28
Status epilepticus		Carbamazepine	1
		Sodium valproate	1
		Sodium valproate+clobazam	1
		Levetiracetam+clobazam	1
		Levetiracetam+phenytoin	1
		Phenytoin+clobazam	1
		Sodium valproate+phenytoin+lorazepam	1
		Lorazepam+clobazam+phenytoin	1

		Levetiracetam+phenytoin+lorazepam	1
		Brivateracetam+clobazam+levetiracetam	1
Febrile seizure		Lorazepam+sodium valproate	3
		Sodium valproate+clobazam	4
		Clobazam	11
		Clobazam+phenytoin	1
		Phenobarbital	2
		Lorazepam+ phenytoin	1
		Phenytoin	1
		Lorazepam+ clobazam	1
		Phenytoin+levetiracetam	1
		Total	25
Total			150

Distribution based on drugs for types of epilepsy

Figure 3 shows that for partial seizures sodium valproate (28.53%, Phenytoin 28.57%) are most commonly prescribed and Lorazepam is least frequently used at 14.29%).

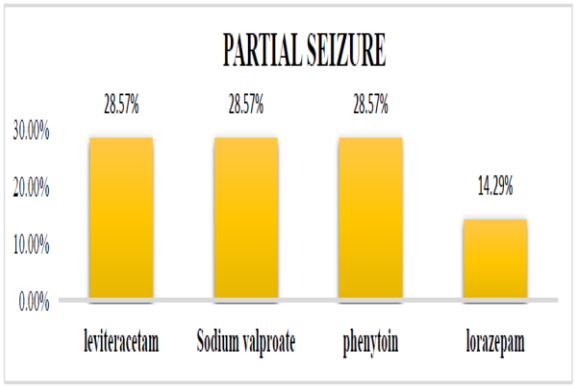

Fig. 3: Partial Seizure.

Figure 4: For generalized seizures, phenytoin was the most commonly prescribed medication, followed by levetiracetam, sodium valproate, phenobarbital, lorazepam, clobazam, carbamazepine, and Lamotrigine.

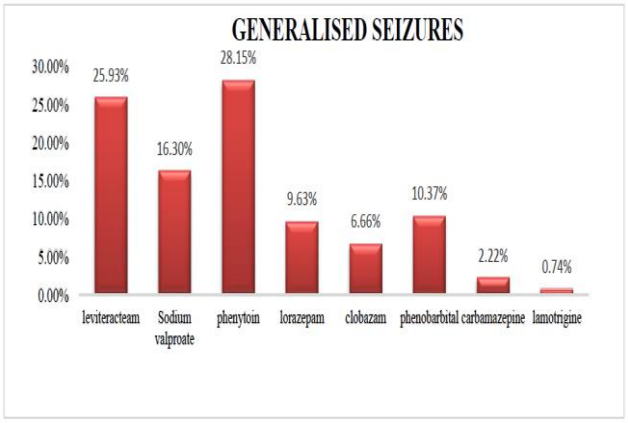

Fig. 4: Generalised Seizure.

Figure 5: For unclassified seizures, the most commonly prescribed antiepileptic drug was phenytoin (37%), followed by Levetiracetam (23%), sodium valproate (16%), lorazepam (16%), clobazam (4%), phenobarbital (2%). and carbamazepine (2%).

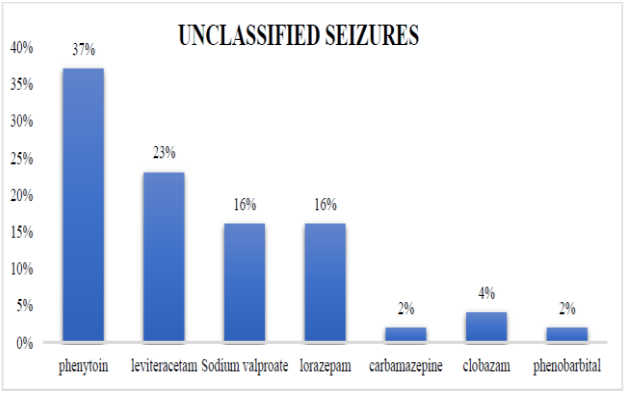

Fig. 5: Unclassified Seizure.

Figure 6: Clobazam is the most commonly prescribed medication for status epilepticus, followed by Levetiracetam, phenytoin, sodium valproate, lorazepam, carbamazepine, and brivaracetam.

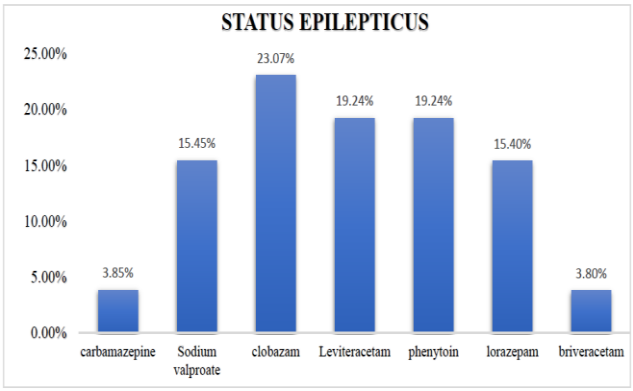

Fig. 6: Status Epilepticus.

Figure 7: Clobazam (47.23%) was most commonly prescribed for febrile seizures, followed by sodium valproate (19.45%), lorazepam, phenytoin, phenobarbital and Levetiracetam.

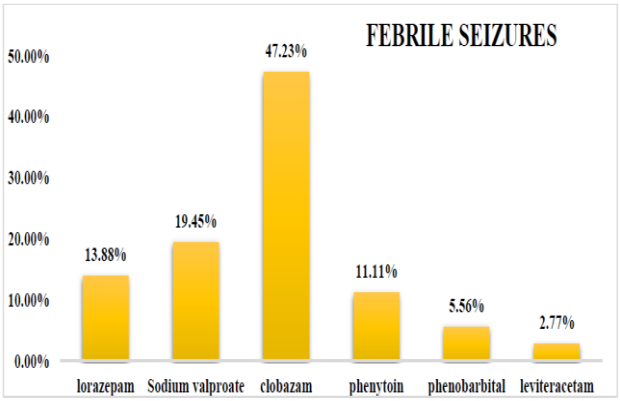

Fig. 7: Drugs used for febrile seizure.

Distribution based on antiepileptic drugs prescribed

A grand total of 253 drugs were prescribed among the 150 patients to manage their epilepsy. The most commonly prescribed antiepileptic drugs were phenytoin (26.49%), Levetiracetam (21.34%), sodium valproate (17%), clobazam (13.43%), and lorazepam (12.25%). Phenobarbital (6.72%), carbamazepine (1.97%), Lamotrigine (0.4%), and brivaracetam (0.4%) were also prescribed, but less frequently. These drugs belong to different classes, such as hydantoin, new generation antiepileptic, aliphatic carboxylic acid, benzodiazepine, barbiturates, iminostilbine, and phenyltriazine.

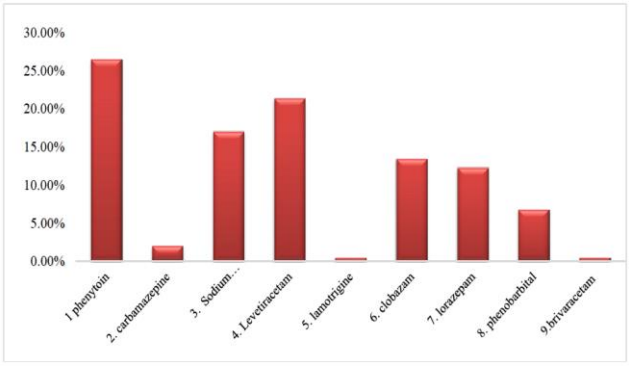

Fig. 8: Distribution based on antiepileptic drugs prescribed.

Distribution based on type of therapy

The study findings indicated that the majority of cases relied on antiepileptic drugs as monotherapy instead of using dual therapy or polytherapy. In terms of treatment, it was discovered that monotherapy was administered to 45.33% of the patients, while dual therapy was given to 42% of the individuals. Additionally, a smaller portion of 12.66% of the patients received polytherapy.

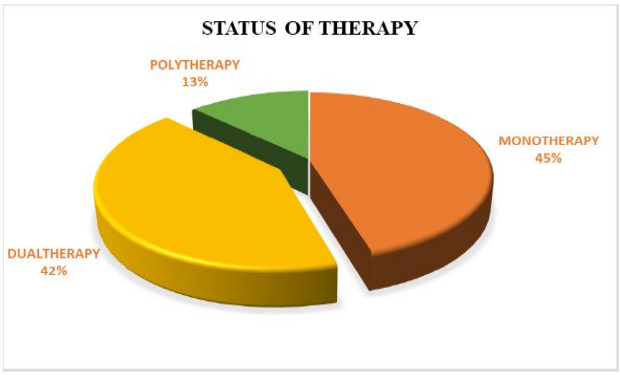

Fig. 9: Distribution based on type of therapy.

Generation of antiepileptic agents

It shows that 197 (77.86%) older generation antiepileptic drugs are prescribed more often than 56 (22.14%) new generation antiepileptic drugs.

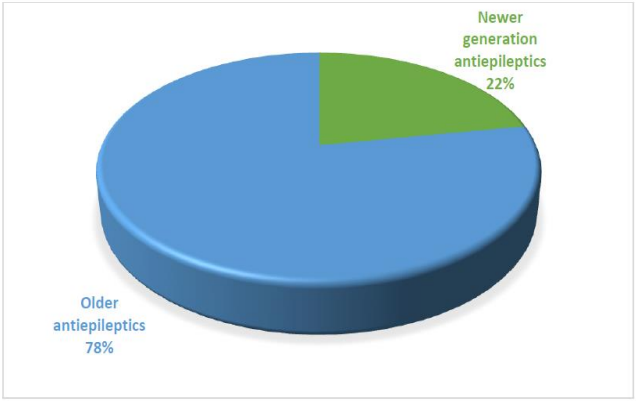

Fig. 10: Generation of antiepileptic agents.

Drug-Drug Interactions

Figure 11(a): Based on our study, there were 69 (73%) moderate interactions, more than 13 (14%) major and 12 (13%) minor interactions.

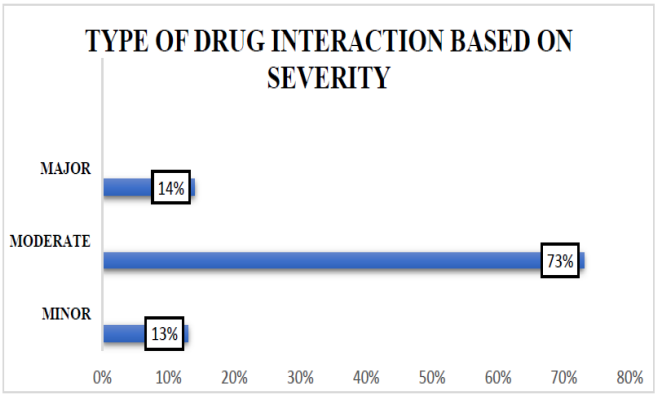

Fig. 11(a): Drug Interaction based on severity.

Figure 11(b): Among the 150 patients assessed, it was found that 56 individuals did not experience any drug interactions. However, 94 patients did encounter drug interactions, which comprised both pharmacodynamic and pharmacokinetic interactions. Notably, the number of pharmacokinetic interactions (84 individuals, representing 89%) surpassed the number of pharmacodynamic interactions (10 individuals, representing 11%).

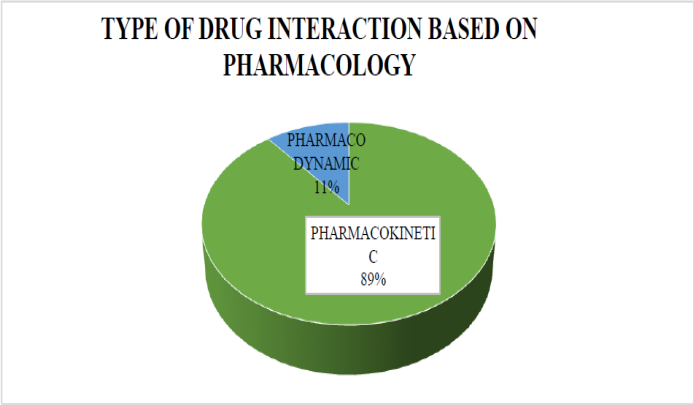

Fig. 11(b): Drug interaction based on pharmacology.

Representation of various type of drug interaction

Table 4: Representation of various type of drug interaction.

Objective drug	Precipitated drug	Frequency	Type
Cyclophosphamide	Phenytoin	1	Major
Carvedilol	Sodium valproate	2	Major
Dexamethasone	Phenytoin	4	Major
Lorazepam	Metoclopramide	1	Major
Phenytoin	Calcium carbonate	2	Major
Nifedipine	Phenytoin	1	Major
Lamotrigine	Sodium valproate	1	Major
Sodium valproate	Meropenem	1	Major
Metronidazole	Phenytoin	10	Moderate
Acyclovir	Phenytoin	4	Moderate
Acetaminophen	Phenytoin	8	Moderate
Lorazepam	Sodium valproate	6	Moderate
Dexamethasone	Phenobarbital	1	Moderate
Linezolid	Phenytoin	1	Moderate
Trihexyphenidyl	Sodium valproate	2	Moderate
Atorvastatin	Phenytoin	9	Moderate
Clobazam	Theophylline	1	Moderate
Levofloxacin	Phenytoin	1	Moderate
Azithromycin	Phenytoin	1	Moderate

Mefloquine	Phenytoin	1	Moderate
Aspirin	Sodium valproate	1	Moderate
Phenytoin	Sodium valproate	3	Moderate
Phenobarbital	Sodium valproate	8	Moderate
Amitriptyline	Clobazam	1	Moderate
Phenytoin	Clobazam	2	Moderate
Sodium valproate	Acyclovir	2	Moderate
Phenytoin	Clopidogrel	1	Moderate
Folic acid	Phenytoin	2	Moderate
Phenytoin	Fluconazole	1	Moderate
Acetaminophen	Carbamazepine	1	Moderate
Carbamazepine	Levetiracetam	1	Moderate
Phenytoin	Ranitidine	4	Minor
Phenytoin	Aspirin	4	Minor
Phenytoin	Phenobarbital	3	Minor
Furosemide	Phenytoin	1	Minor
Total drug interaction		94	

Medication adherence behaviour (Mmas-8)

It showed that out of 150 patients, most of the patients (50%) had low compliance (0-4), while medium (5-6) compliance was 33.33% of patients and good compliance was 16.66% of patients. A total of 150 patients, of which 96 men follow less medication than 54 women.

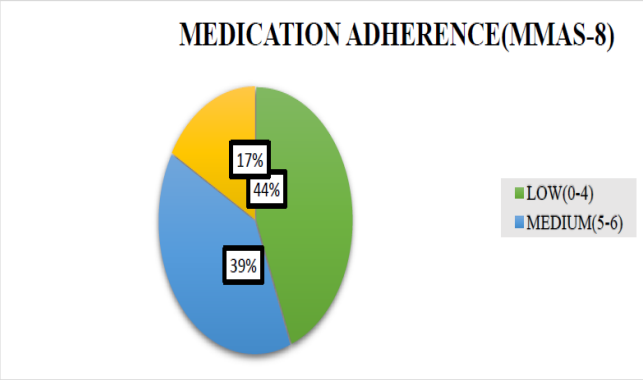

Fig. 12: Medication adherence behaviour (mmas-8).

DISCUSSION

Distribution of sample according to demographic data

In our study, the majority (24%) of these patients were in the age range of 36 to 60. This discovery was corroborated by Arulkumaran et al.[14] There were 23 studies done in Coimbatore, and 48% of the patients were between the ages of 31 and 60. 17.33% of the subgroup of epileptic patients (toddlers) was between the ages of 1 and 3 years. It contrasts with western research, though, such as those by Loiseau et al,[15] Hauser et al,[16] and Sidenvall et al,[17] which found a higher prevalence of epilepsy at extreme ages. The least number of patients were those between the ages of 0 days and 1 month. In our study population, there were 64% more men than women (36%), or approximately two times as many men as women. Contrary to our findings, T. Badwaik et al.[18] observed that females in their study were exposed to antiepileptic medicines at a higher rate than males; nevertheless, Murthy NV et al.[19] Our finding is supported by studies by Juny Sebastian et al.[20] and Jena M et al.[21] which found that males were more commonly assaulted by epilepsy than females.38.66% of the study's participants were uneducated. Pediatric age groups from 0 to 5 years old and illiterate adult patients were included in the category of uneducated status. Ismael Ahmed et al[22] also demonstrates that 95 (32%) of the study participants were illiterate, which is similar to our findings.

Distribution of sample according to comorbidities

Out of 150 patients, epilepsy due to co-morbidities (67.33%) was more in our study. Out of 16 comorbid conditions neurological disorders 24(23.76%) were highest followed by hypertension 15(14.85%), CVA/stroke 13(12.87%), RTI 10(9.9%). Juny Sebastian et. al[20] also seen hypertension as most common comorbidity like our study. Study from Germany, Shackleton et.al[23] found Cerebrovascular Accident, dementia, and intra cerebral hematoma as a most common comorbidity.

Distribution of sample according to etiology

Out of 10 etiological conditions, neurological disorders 35(23.33%) were highest followed by fever 31(20.66%), poor drug compliance 28(18.67%), CVA/stroke and

syncopal attack 21(14%), which contradicts the study of Jena M et .al[21] and Mazhar et. Al.[24] Among the highest etiology (neurological disorders), includes neuroinfections, microcephaly, brain structure abnormalities and cerebral palsy etc.

Distribution of sample of patients according to type of seizures

In our study GTCs (55.33%) was the most occurred type of seizure which is similar to the study conducted by Arulkumaran et. Al,[14] Jincy George et. Al,[25] Akinsulore A et. Al[26] and Alan George et. Al.[27] However, it contradicts the Patel et.al[28] Studies with a higher prevalence of partial seizures than generalized seizures. But third most occurred type of seizure was a febrile seizure (16.66%). This is because our study enrolled pediatric patients who were more prone to febrile seizures.

AED Utilization

In epileptic patients Phenytoin accounted highest utilization rate (26.49%) followed by Levetiracetam (21.34%). The highly used AEDs among the study population were phenytoin (28.15%) and Levetiracetam (25.93%), both were mainly used for generalized seizures, which is similar in Jincy George et.al[25] studies.A study conducted by Juny Sebastian et.al[20] and Alan George et. Al[27] has a similar drug use profile i.e., Phenytoin was frequently prescribed drug, but this was in contrast to the study conducted by Mazhar et. Al[24] because Sodium valproate 16.8% was the most commonly prescribed AED followed by Diazepam 14.4% and Phenytoin 13%. Recently published studies, Murthy et.al[19] Arul Kumaran ET. Al,[14] Johannessen et. Al,[29] Pathak et. Al[30] Malerba et. Al[31] mention that Sodium Valproate was the most common drug prescribed followed by Phenytoin or other drugs. An Indian study by Thomas SV et. al 200[32] mentioned that Carbamazepine was prescribed most commonly.

Distribution of AEDs According To Status of Therapy

Monotherapy was practiced in 45.33% of our patients and dual therapy 42% and polytherapy 12.66%, which was similar in many studies, Murthy et.al 19, Arulkumaran et. Al,[14] Malerba et.al[31] and Shobhana et. Al[33] with its many advantages. Nevertheless, multiple drug therapies were unavoidable in some patients, even though Polypharmacy adversely affect the quality of life. In 63 (42%) patients, seizures were managed with dual therapy (Akhiyani et. Al.[34] Polytherapy should be considered when failure of two attempts of monotherapy. In our study up to 4 different antiepileptic drugs were prescribed in a prescription at maximum but polytherapy 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. Failure of monotherapy may also result from lack of adherence resulted from no proper counselling about their medication to the rural patient.

Generation of Anti-Epileptic Agents

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 antiepileptic drugs. (Arulkumaran et.al[14]). Most of the epileptic patients were effectively managed with conventional or older AEDs like Phenytoin, Carbamazepine, Sodium Valproate, Phenobarbital, Clobazam and Clonazepam as observed in the earlier studies (Rishel et. Al,[35] Loiseau P et. Al[15]). The highly used AEDs among the study population were Phenytoin (26.49%), Levetiracetam (21.34%) and Sodium Valproate (17%). The study is similar to Jincy George et. Al,[25] Arulkumaran et. Al[14] and Patel et.al studies.[28] The newer AEDs – Levetiracetam, Brivaracetam and Lamotrigine were used in a lesser extent as compared to older anti epileptics which is in contrast to study conducted by Gunindro et. Al.[36]

Drug Interactions

In our study, about 94 drug interactions were identified and were categorized as moderate 69(73%), major 13(14%), minor 12 (13%). All these interactions were potential interactions.20 were found to be AED+ AED interactions and 74 were AED +other drugs. Out of this, we observe that, there was no major interaction involving AED+AED and those were moderate interactions which contradict the study of Alan Raju George et. Al[27] There is two mechanisms by which drug-drug interaction may take place. They are pharmacodynamic (11%) and pharmacokinetic mechanism (89%). Phenytoin was mostly interacting with number of other drugs through enzyme induction. Likewise, Metronidazole plus Phenytoin accounted for frequently encountered drug interaction in our settings.

Medication adherence

This cross-sectional study assessed the level of medication adherence to AED among patients with epilepsy and show that 44% of study participants were low adherent to anti-epileptic medications, from which males are more followed by medium adherence (39%) and high adherence (17%). Our finding showed that the issue of low adherence is not changing in India. These were the poor adherence groups. So, we counselled them to improve further of their medication adherence behavior. Base line follows up to see the outcome however was not done. In these instances, patients will realize the benefits of adherence only as time passed because they learn from their personal experience. WHO, Sweileh WM et .al 63 also reported that patients with busy lifestyles commonly do not adhere to medication.

CONCLUSION

Our data indicates that neurological disorders were main offender of symptomatic epilepsy in our study generalized seizures were most prominent followed by unclassified seizures. Simple febrile seizures were the

commonest of epilepsy recorded in pediatric patients. Most of patients were adult and epileptic seizures were more common in male. Among the study population, some responded to monotherapy while others required combination therapy due to the seizure type and co-morbid conditions. The drugs prescribed were mainly from the essential drug list. The most commonly prescribed AEDs as Phenytoin, followed by Levetiracetam, Sodium Valproate etc. for epilepsy. Phenytoin is broad spectrum antiepileptic most commonly used for partial onset seizure as well as generalized clonic tonic seizures. Being cheap, 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. We also witnessed the fact that majority of patient are not aware of how to administer different dosage forms. Nowadays, multiple AED's are available, and the best antiepileptic therapy is to ensure optimal seizure control.

There was underutilization of newer AEDs. Inclusion of newer AEDs like Lamotrigine, Levetiracetam, brivaracetam etc. in the essential drug list was recommended. Older antiepileptic drugs were still commonly prescribed. Problems in polytherapy is due to 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 is needed if necessary. The finding of our study concluded that drug-drug interactions were quite common in the prescription of seizure disorder in our study, therefore it is important to closely monitor and identify the drug related problems that are related to AEDs, thus to improve the quality of treatment. Polypharmacy can predispose to drug interactions which results in the failure of the drug therapy and increase in the length.

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