



Drug utilization study of antiepileptic drugs in the pediatric department in a tertiary care hospital

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Abstract

Background: Epilepsy is basically any disorder characterised by uncontrolled excessive and synchronous electrical discharges in various brain areas resulting in spontaneously recurrent seizures which typically last from seconds to minutes. For the rationale drug use and to suggest measures to change prescribing habits for the better management of epileptic seizures it is very necessary to know the prescription pattern of these drugs. This study aims to study the utilisation pattern of antiepileptic drugs in paediatric patients in a tertiary care hospital.

Methods: The present retrospective observational study was conducted at Daya Hospital, Thrissur. Ninety six Paediatric patients of either gender diagnosed to had epilepsy and taking treatment from Daya Hospital were included in the study. Patient's detailed medical history, demographic details and other required information was recorded.

Results: The study showed that out of 96 patients typical febrile seizure (73%) was found to be the most common form of seizure among paediatric patients of age group 1- 5 years of age. Clobazam was the most commonly prescribed (71%) AED followed by midazolam (69%). 27% patients were prescribed monotherapy. Clobazam + Midazolam was the most commonly (31%) used combination.

Conclusion: From this study it was found that majority of prescription was without a generic name. It was concluded that Clobazam was the highly prescribed drug followed by Midazolam. There was no any serious drug drug interactions. There is a need for further up-to-date studies to determine the drug utilisation pattern of paediatric patients.

Keywords: Epilepsy; Seizure; Paediatric; Antiepileptic Drug (AED)

1. Introduction

Drug Utilization Research is defined by WHO in 1977 as "The marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences." The principle aim of the drug utilization research is to facilitate rationale use of drugs in populations. For the individual patients, rationale use of a drug implies the prescription of a well documented drug in an optimal dose for a right indication, with the correct information and at an affordable price. Without the knowledge of how drugs are being prescribed and used, it is difficult to initiatediscussion on rationale drug use and to suggest measures to change prescribing habits for the better management. Information on the past performance of prescribers is the linchpin of any auditing system. Drug utilization research is also referred as Drug utilization evaluation (DUE) or Medication use evaluation (MUE) [1,2].

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1.1. Scope of drug utilization studies

Drug utilization studies may include descriptive epidemiological approaches to the study of drug utilization, but also the assessment of how drug utilization relates to the effects of drug use, beneficial or adverse. The research in this field aims to analyze the present state and the developmental trends, of drug usage at various levels of the health care system, whether national, regional, local or institutional. Drug utilization studies may evaluate drug use at a population level, according to age, sex, social class, morbidity, among other characteristics[3,4].

1.2. Classification of drug utilization evaluation

DUR is typically classified into three different categories,

- PROSPECTIVE DUR: Prospective review evaluating a patient's planned drug therapy before a medication described. This DUR helps the pharmacist to access the prescription medication dosage, drug interactions and resolve drug related problems.
- CONCURRENT DUR: It is performed during the course of treatment and the ongoing monitoring of drug therapy for the positive patient outcomes.
- RETROSPECTIVE DUR: It is a review of drug therapy after the patient has received the medication. A retrospective review aims to detect the pattern in prescribing, dispensing or advertising drugs and it helps to prevent recurrence of inappropriate medication use. The advantage of this DUR is ease of data collection, as records are assessed at the data collector's convenience. A disadvantage is that some information may be unclear or missing and the reviewed patients may not gain immediate benefit, as interventions are delayed until the intervention phase[5].

1.3. Steps in establishing a drug utilization program

Utilization evaluation process is divided into four phases

1.3.1. Phase 1: Planning

- Develop a DUR Committee.
- Write policies and procedures.
- Describe about the departments of the hospital, where drug are utilized (intensive care unit, radiology, surgical department, medical department).
- Select specific drugs for possible inclusion in the program.
- Assess resources available for criteria development, data collection, and evaluation. Consider the indications, dosing, dosage form, frequency of drug used to monitor and evaluate.
- Select criteria and establish performance thresholds.
- Develop the methodology for data collection, evaluation and create a schedule.
- Educate hospital staff about Drug utilization evaluation study and current criteria.

1.3.2. Phase 2: Data Collection and Evaluation

- Start the data collection in a proper way.
- Evaluate the collected data and determine if drug use problems exist.

1.3.3. Phase 3: Intervention

- Send the results to hospital staff.
- If a drug use problem was found, design and implement interventions.
- Collect new data on problem drug to determine if drug use has improved as a result of the intervention.
- Disseminate results of re-evaluation.

1.3.4. Phase 4: Program Evaluation

- Evaluate all DUR program activities at the end of the year, and plan the new activities for the upcoming year[6,7,8].

1.4. Epilepsy

There are over 2.5 million people diagnosed with epilepsy every year. Epilepsy is one of the most common serious neurological disorders affecting about 65 million people globally. It affects 1% of the population by age 20 and 3% of

the population by age 75. It is more common in males than females with the overall difference being small. Most of those with the disease (80%) are in the developing world. Epilepsy is usually present in childhood or adolescence but may occur for the first time at any age. About 5% of the population suffers a single seizure at some time. About 0.5-1% of the population have recurrent seizure epilepsy. About 70% patients are well controlled with drugs (prolonged remissions) and 30% epilepsy patients are at least partially resistant to drug treatments[9,10,11].

According to the World Health Organization, “epilepsy refers to a group of chronic brain conditions characterized by recurrent epileptic seizures”. These seizures are the clinical manifestations of excessive and hyper-synchronous, usually self-limited, abnormal activity of neurons in the brain. Seizure is the transient occurrence of signs and symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain. Signs or symptoms may include alterations of consciousness, motor, sensory, autonomic, or psychic events[12,13,14].

Table 1 Type of seizure and symptoms

Types of seizures		Symptoms
Generalized seizures (Produced by the entire brain)	Grand Mal or Generalized tonic-clonic	Unconsciousness, convulsions, muscle rigidity.
	Absence	Brief loss of consciousness.
	Myoclonic	Sporadic (isolated), jerking movements
	Clonic	Repetitive, jerking movements.
	Tonic	Muscle stiffness, rigidity.
	Atonic	Loss of muscle tone.
Focal (partial seizures Produced by a small area of the brain)	1. Simple (awareness is retained)	
	a. Simple motor	Jerking, muscle rigidity, spasms, head-turning
	b. Simple sensory	Unusual sensations affecting either the vision, hearing, smelltaste, or touch.
	c. Simple psychological	Memory or emotional disturbances
	2. Complex (Impairment of awareness)	Automatisms such as lipsmacking, chewing
	3. Partial seizure with secondary generalization	Symptoms that are initially associated with a preservation of consciousness that then evolves into a loss of consciousness and convulsions
Unclassified seizures	Neonatal seizures Infantile spasms ^[15]	

1.4.1. Causes of Seizures

Seizures occur because small numbers of neurons discharge abnormally. Anything that disrupts the normal homeostasis of the neuron and disturbs its stability may trigger abnormal activity and seizures. A genetic predisposition to seizures has been suggested. The causes of seizures in the elderly may be multifactorial and include cerebrovascular disease (both ischemic and hemorrhagic stroke), neurodegenerative disorders, tumor, head trauma, metabolic disorders, and CNS infections. In some cases, if an etiology can be found and corrected, the patient will not require chronic AED treatment. The incidence of idiopathic epilepsy is higher in children. Many factors have been shown to precipitate seizures in susceptible individuals. A careful history should be obtained from patients presenting with seizures because theophylline, alcohol, high dose phenothiazines, antidepressants (especially maprotiline or bupropion), and street drug use have been associated with provoking seizures. Children who are small for gestational age or with neonatal seizures are also at increased risk for developing epilepsy. The most clearly established risk factors for epilepsy in all age groups are head trauma (especially in patients in whom the duramater has been breached and in whom there is evidence of loss of consciousness), CNS infections, and stroke. Immunizations have not been associated with an increased risk of epilepsy[9,11,13].

1.4.2. Pathophysiology

Seizures result from excessive excitation, or from disordered inhibition of population of neurons. Initially, a small number of neurons fire abnormally. Then normal membrane conductance and inhibitory synaptic currents break down, excitability spreads locally (focal seizure) or more widely (generalized seizure).

Mechanisms that may contribute to synchronous hyper excitability include:

- Alterations of ion channels in neuronal membranes.
- Biochemical modifications of receptors
- Modulation of second messaging systems and gene expression
- Changes in extracellular ion concentrations
- Alterations in neurotransmitter uptake and metabolism in glial cells
- Modification in the ratio and function of inhibitory circuits
- Local neurotransmitter imbalance (e.g. glutamate, γ aminobutyric acid [GABA]).

Large numbers of generalized tonic-clonic (GTC) seizures (more than 100) and multiple episodes of status epilepticus may be associated with neuronal damage. In particular, continued exposure to glutamate may contribute to neuronal damage [12,16].

1.4.3. Classification of Epileptic Seizures:

Epileptic seizures are classified as either focal or generalized, based on how the abnormal brain activity begins.

Focal or Partial Seizures:

When seizures appear to result from abnormal activity in just one area of brain, they are called focal (partial) seizures. These seizures fall into two categories.

- Simple focal seizures: These seizures do not result in loss of consciousness. They may alter emotions or change the way things look, smell, feel, taste or sound.
- Complex partial seizures: Complex partial seizures are characterized by focal seizure activity accompanied by a transient impairment of the patient's ability to maintain normal contact with the environment. The patient is unable to respond appropriately to visual or verbal commands during the seizure and has impaired recollection or awareness of the ictal phase.
- Dyscognitive focal seizures: These seizures alter consciousness or awareness and may cause to lose awareness for a longer period of time. Dyscognitive focal seizures often result in staring and purposeless movements such as hand rubbing, chewing, swallowing or walking in circles.

Generalized Seizures (Convulsive or Non-convulsive)

Seizures that appear to involve all areas of the brain are called generalized seizures. Six types of generalized seizures exist.

- Absence seizures (Petit Mal): Petit Mal or Absence seizures are characterized by staring and subtle body movement. These seizures can cause a brief loss of awareness.
- Tonic seizures: Tonic seizures cause stiffening muscles. These seizures usually affect muscles in back, arms and legs and may cause to fall to the ground.
- Clonic seizures: Clonic seizures are associated with rhythmic, jerking muscle movements. These seizures usually affect the neck, face and arms.
- Myoclonic seizures: These usually appear as sudden brief jerks or twitches of arms and legs.
- Atonic seizures: Atonic seizures, also known as drop seizures, because a loss of muscle control, which may result in suddenly collapse or fall down.
- Tonic-clonic seizures (Grand Mal): Tonic-clonic seizures are characterized by a loss of consciousness, body stiffening and shaking, and sometimes loss of bladder control or biting tongue.

Status epilepticus is defined as either continuous seizure lasting at least for 5 minutes, or two or more discrete seizures between which there is incomplete recovery of consciousness.

Febrile seizures occur in up to 8% of children between 6 months and 6 years of age. Long term treatment or prophylaxis for simple febrile seizures is not recommended. Unclassified epileptic seizures: Not all seizure types can be classified as

partial or generalized. This appears to be especially true of seizures that occur in neonates and infants. The distinctive phenotypes of seizures at these early ages likely result, in part, from differences in neuronal function and connectivity in the immature versus mature CNS[15].

A febrile seizure is defined as a “seizure in association with a febrile illness in the absence of CNS infection or acute electrolyte imbalance in a child older than 6 months of age without prior afebrile seizures.” 4 Important things to remember are that a fever may not be present at time of seizure, febrile seizures can occur in any child, and febrile seizures are most common between ages 6 months and 6 years. The peak incidence of febrile seizures is age 18 months, and onset after age 7 is very uncommon[17,18].

A simple febrile seizure is an isolated brief generalized seizure, while a complex febrile seizure occurs when the seizure is prolonged (greater than 10 or 15 minutes) or there are multiple seizures within same febrile illness. Risk factors for febrile seizures include a first- or second-degree relative with a history of febrile seizures, a neonatal nursery stay of more than 30 days, a developmental delay, and attendance at day care. When a child presents with a febrile seizure, acute management mandates that serious conditions, including meningitis, encephalitis, electrolyte imbalances, and other acute neurologic illnesses, are sought first. The American Academy of Pediatric guidelines suggest a lumbar puncture be strongly considered in children younger than 12 without an obvious source of the fever, children with a first complex febrile seizure, children with persistent lethargy, or children recently receiving antibiotics. An MRI or CT scan is not necessary for simple febrile seizures, and an EEG is of limited value with a simple febrile seizure. An EEG can be considered if the seizure was complex, there is a family history of epilepsy, or there are pre-existing developmental abnormalities[19,20,21].

1.4.4. Tests and Diagnosis

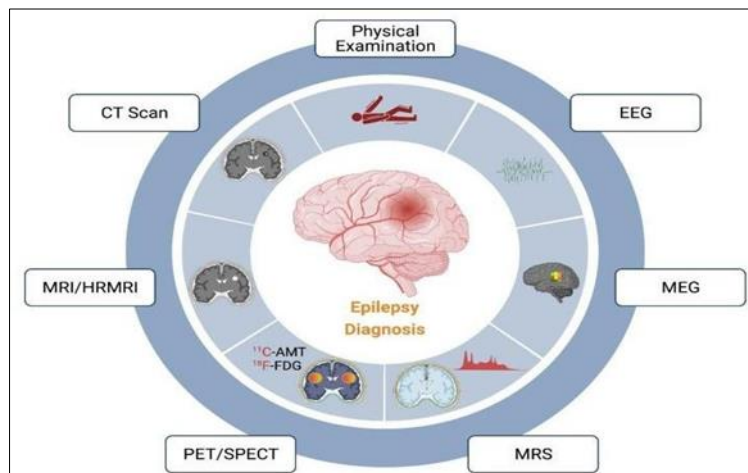


Figure 1 Tests and Diagnosis of Epilepsy

Physical Examination

Physical examination helps in the diagnosis of specific epileptic syndromes that cause abnormal findings, such as dermatologic abnormalities. In addition, patients who for years have had intractable generalized tonic-clonic seizures are likely to have suffered injuries requiring stitches. Several tests to diagnose epilepsy and determine the cause of seizures includes Neurological examination: A neurological examination looks at how well brain and the rest of nervous system are functioning and may test behaviour, motor abilities, mental function and other areas to diagnose condition and determine the type of epilepsy. Blood tests: There are a number of blood tests that may be recommended to check for signs of infections, genetic conditions or other conditions like electrolyte imbalances which may be associated with seizures.

Electroencephalogram (EEG)

An electroencephalography test can help to diagnose a seizure. These tests measure brain waves. Viewing brain waves during a seizure can help to diagnose the type of seizure. An EEG gives information about the electrical activity of the brain during the time the test is happening.

Neuroimaging

Imaging scans such as a Computerized tomography (CT) scan, Magnetic resonance imaging (MRI), Functional MRI (fMRI), Single-photon emission computerized tomography (SPECT) also can help by providing a clear picture of the brain. Functional neuroimaging provides further information and may show abnormalities even in cases where MRI was normal, thus further helping in the localization of the epileptogenic foci and guiding the possible surgical management of intractable/refractory epilepsy when indicated.

Neuropsychological Tests

These tests are performed to assess thinking, memory and speech skills. The test results help to determine which areas of brain are affected^[15].

1.4.5. Treatment of seizure

The majority of epileptic seizures are controlled through drug therapy, particularly anticonvulsant drug. The type of treatment prescribed will depend on several factors including the frequency and severity of the seizures as well as the person's age, overall health, and medical history. An accurate diagnosis of the type of epilepsy is also critical to choosing the best treatment.

Antiepileptic drugs

The different antiepileptic drugs (AEDs) act by affecting one or more of these processes. Specific mechanisms of action of the AEDs include:

- Modulation of voltage dependent ion channels: Carbamazepine, Phenytoin, Valproic acid.
- Enhancement of activity of the major inhibitory neurotransmitter in the brain, GABA: Phenobarbital, Benzodiazepines, Tiagabine.
- Suppression of excitatory neuro-transmission: Lamotrigine, Felbamate.

Surgery

Surgery includes removal of the area of brain causing the seizures.

Vagus nerve stimulation

The vagus nerve is stimulated to reduce the frequency and intensity of seizures. This can be suitable for some people with seizures that are difficult to control with medication.

Ketogenic diet

A diet very high in fat, low in protein and almost carbohydrate free. This can be effective in the treatment of difficult to control seizures in some children.^[15]

2. Material and method

2.1. Study Site

DAYA Hospital, Thrissur

2.2. Study Design

Retrospective observational study

2.3. Duration of Study

2 months duration from May 2023 to June 2023

2.4. Sources of Data

- Specially Designed data collection form.
- Physicians prescribing records.
- Patient's medication profile.

- Patient profile (age, sex, weight, height, patient's address).
- Drugs prescribed (generic/brand name).
- Doses and frequency of drugs.

2.5. Parameters for Evaluation

- Average number of drugs per encounter.
- Percentage of drugs prescribed by generic name.
- Percentage of encounters with injection prescribed.
- Percentage of drugs prescribed from essential drug list.

2.6. Sample size calculation

$$\begin{aligned}n &= (z_{1-\alpha/2})^2 p (1-P) / d^2 \\ &= (1.96)^2 2.4637(1-.4637)/(.1 \times .1)^2 \\ &= 95.49\end{aligned}$$

$$= 96 [+9] \text{ dropout Minimum 96 sample required}$$

d=Margin of error (10%) P=Prevalence from previous study $Z_{1-\alpha/2}$ =Significance level=5%=1.96

2.7. Study criteria

2.7.1. Inclusion criteria

Age 0-12, paediatric patients with epilepsy

2.7.2. Exclusion criteria

- HIV/AIDS paediatric patients
- Children who were seriously sick (ICU, emergency)
- Hepatic and renal disease with co-morbidity
- Psychogenic non-epileptic seizure, provoked seizures potentially caused by drug abuse.
- Previous traumatic head injury, primary brain tumour, and brain metastases. Allergy to any of the trial medication

3. Results and discussion

3.1. Patient demographic data

3.1.1. Demographic Character

Out of 96 patients satisfying the inclusion and exclusion criteria 53(55%) were males and 43(44%) were females .

3.1.2. Age wise distribution

The highest number of patients, 82 (85%) were in the age group 1-5 years followed by (8%) from less than 1year and the lowest number of patients (6%) were in the age group 6-12 years .

3.1.3. Distribution according to type of epilepsy

From this study Generalised seizure was the most commonly observed seizure. In this febrile seizures were very common. Out of 96 patients (73%) were treated for Typical febrile seizure followed by (11%) Complex febrile seizure, (2%) Atypical febrile seizure, (5%) Acute febrile seizure (4%) Typical symptomatic seizure and (4%) was treated for other seizure disorder (Table no.6).

Table 2 Distribution according to type of epilepsy

Sl. No	Disorder	No. of patients	Percentage
1	Typical febrile seizure	70	73%
2	Complex febrile seizure	11	11%
3	Atypical febrile	2	2%
4	Acute febrile seizure	5	5%
5	Typical symptomatic seizure	4	4%
6	Seizure disorder	4	4%

3.1.4. Categories of drugs

Table 3 Categories of drugs

Sl. No	Classes of drugs	Total no. of Drugs	Percentage
1	Antiepileptic	183	190%
2	Anti Histamine	61	63%
3	Bronchodilator	68	70%
4	NSAID	88	91%
5	Expectorant	68	70%
6	Antibiotic	89	92%
7	others	245	255%

From the study it was found that, the most frequently used classes of drugs was found to be Probiotic (93%) followed by Antibiotic (92%), NSAID (91%) Bronchodilator and Expectorant (70%), Antihistamine (63%) . (Table no.7)

3.1.5. Prescribing frequencies of selected drugs

Table 4 Prescribing frequencies of selected drugs

Sl. No	Antiepileptic drugs	Total no. of patient	Percentage
1	Clobazam	69	71%
2	Midazolam	67	69%
3	Sodium Valproate	2	2%
4	Levetiracetam	43	44%
5	Oxcarbazepine	2	2%

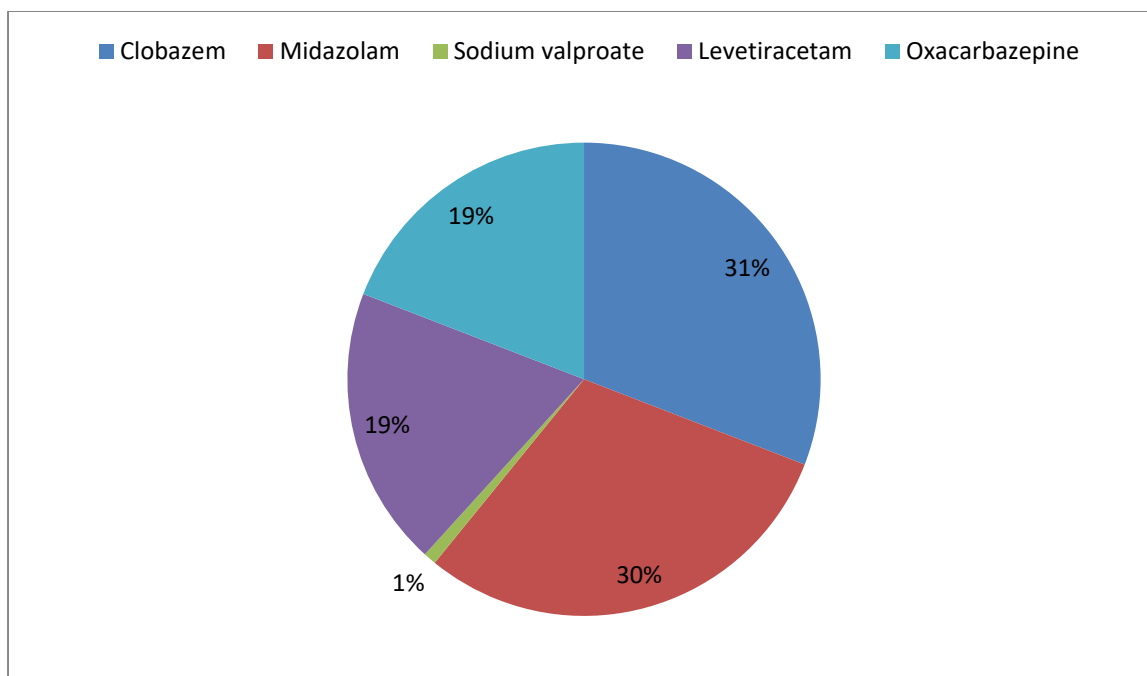


Figure 2 Prescribing frequencies of selected drugs

Out of 96 prescriptions analysed, the most frequently prescribed antiepileptic drug prescribed was found to be Clobazam (71%), followed by Midazolam (69%), Levetiracetam (44%), Sodium valproate(2%), and Oxcarbazepine (2%).

3.1.6. Antiepileptic Monotherapy

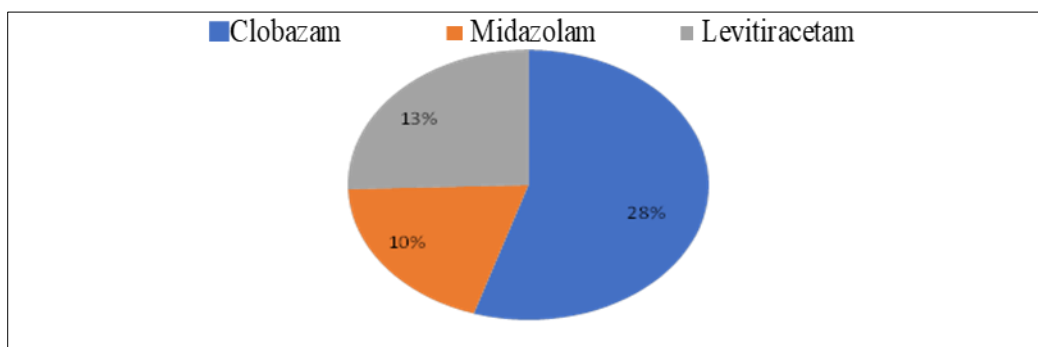


Figure 3 Antiepileptic Monotherapy

Out of 96 prescriptions analysed, clobazam (28%) was the highly prescribed antiepileptic drug as monotherapy followed by levetiracetam (13%) and midazolam (10%)

3.1.7. Antiepileptic Dual therapy

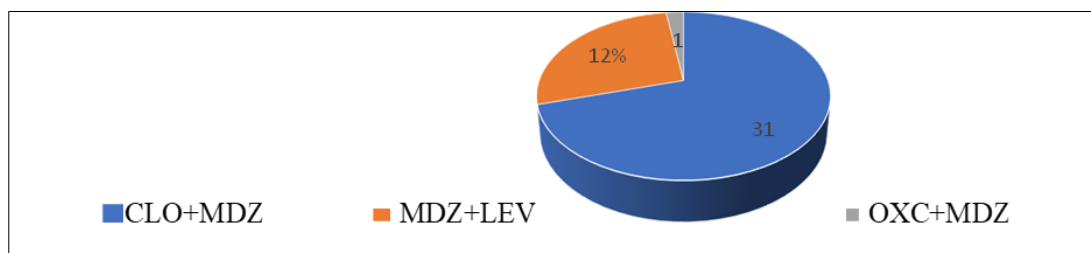


Figure 4 Antiepileptic Dual therapy

Out of 96 patients antiepileptic dual therapy was observed to be given for 43 patients. In this the clobazam+ Midazolam (31%) was the highly prescribed drug followed by Midazolam+levetiracetam (12%), and Oxcarbazepine+ Midazolam (1%) (Table no.10)

3.1.8. Antiepileptic Polytherapy

From the study it was found that antiepileptic drug polytherapy was only (1%) clobazam + Midazolam+ Sodium valproate

3.1.9. Most commonly used Antihistamine

Among the total drug prescribed 34 single antihistamines were used. In this cetirizine (11%) was the most commonly used antihistamine followed by levocetirizine (7%), phenylephrine and chlorpheniramine (4%), xylometazoline, fexofenadine and oxymetazoline (2%) and olopatadine (1%) .

3.1.10. Rationality

Table 5 Rationality

Sl.No	Parameters	Total no. of drugsN=1358	Percentage
1	Drugs prescribed by generic name	440	31%
2	Drugs prescribed by brandname	525	38%
3	Drugs prescribed from national list of essentialMedicines	393	28%

In the study the prescriptions were analyzed for its rationality. Among total 1358 drugs prescribed, (38%) drugs were prescribed by their brand name (31%) drugs prescribed by their generic name. And about (28%) drugs were prescribed from national list of essentialmedicines.

3.1.11. Most commonly used NSAID

Out of the total drugs analysed, 88 drugs were NSAIDS. In this (89%) paracetamol was the most commonly prescribed drug followed by Mefenamic acid (2%) .

3.1.12. Route of administration wise distribution

Out of various routes of administration the major route of administration was by oralroute (83%). The other main routes of administration of drugs were found to be nasal(15%) and parenteral (1%) .

3.1.13. Dosage Form wise distribution

Out of various dosage forms used, suspension was the most commonly prescribed dosageform (36%) followed by syrup (33%), Tablet (17%), and Nasal spray(12%).

3.1.14. Drug interaction

Table 6 Drug interaction

Drug-druginteractions	Type of Interactions	Interactioneffect	Total	Severity
Clobazam+pantoprazole	Pharmacokineticinteraction	Increase plasma levelof clobazam	38	Minor
Lansoprazole+clobazam	Pharmacokineticinteractions	Effect hepaticenzyme	21	Moderate
Oxcarbazepine+ clobazam	Pharmacokineticinteractions	Increase sedation	1	Moderate
Levocetirizine+clobazam	Pharmacodynamicinteractions	Increase sedation	6	Moderate
Pantoprazole +oxcarbazepine	Pharmacodynamicinteractions	Effect hepaticenzyme	1	Moderate

The study observed that in 96 prescriptions, 67 drug interactions were present out of which 38 was minor and 29 was moderate. Further these interactions was categorized as pharmacokinetic and pharmacodynamic. There were 60 pharmacokinetic and 07 pharmacodynamic drug interactions were found in these prescriptions.

List of abbreviation

- AED: Antiepileptic drug
- AIDS: Acquired immunodeficiency syndrome
- CLO: Clobazam
- CNS: Central nervous system
- CT: Computerized tomography
- DUR: Drug utilization research
- EEG: Electroencephalogram
- GABA: Gamma Amino Butyric Acid
- GTC: Generalized Tonic Clonic
- HIV: Human Immuno Deficiency Virus
- LPZ: Lansoprazol
- LEV: Levetiracetam
- MDZ: Midazolam
- MUE: Medication use evaluation
- NSAID: Non Steriodal Anti Inflammatory Drugs
- OCB: Oxycarbazepine
- PET: Positron Emission Tomography
- PNZ: Pantoprazole
- SE: Status Epilepticus
- XMC: Xylometazoline

4. Conclusion

The study results shows that out of 96 patients most of the seizure cases were in males. May be due to increased male to female ratio. The highest number of patients were in the age group 1-5 years. Mostly seen type of seizure was generalized seizure. Mostly prescribed antiepileptic drug was Clobazam followed by Midazolam in this tertiary care hospital. It was concluded that monotherapy of antiepileptic drugs were preferred than dual or polytherapy. It was found that Clobazam and Midazolam combination was mostly preferred antiepileptic drug therapy. Cetirizine was the commonly prescribed antihistamine. Paracetamol was the mostly prescribed NSAID for paediatric epileptic patients. Suspension dosage form was mostly preferred form of dosage. Oral route of drug administration was more preferred in these patients. From this study, it was found that majority of the drug interactions were minor and was between clobazam and lansoprazole while moderate interaction was found between lansoprazole and pantoprazole. The study concluded that majority of prescriptions were without generic names. The study can be made more effective by conducting long term studies to understand the changes in prescription patterns.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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