

Observational Study of Prescribing Pattern of Antiepileptic Drugs in Tertiary Care Hospital

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Abstract

Trial Design: Observational study

Methods

Inclusion criteria: All In-patients who were treated with AEDs admitted in different units of Medicine Department.

Exclusion Criteria: All pregnant women who are on AEDs.

Sample size: 35

Objective: The chief objective behind this project was to observe the various therapy of AED used in epilepsy and in some co-morbid condition and to observe the patient condition.

Outcome

- A total of 35 patients data were recorded in the study for 1 month.
- In the study percentage of men suffering from epilepsy was 45.71% (16) and Female was 54.24 % (19).
- The study shows that most of the patients 14 (40%) were from the age group of 31-60 years; followed by 14 (40%) of patients in the age group of 61-90 years and 7 (20%) patients were in the group of 10-30 year.
- Most commonly prescribed drug concluded is phenytoin which accounts for 30 (85.30%) in both the genders, followed by phenobarbitone 11 (31.18%) and levitracetam usage was 11 (31.18%)
- Monotherapy is the type of therapy most frequently used in 23 patients (65.71%).
- Dual therapy is used in 6 patient (17.14%).Triple therapy is used in 5 patient (14.28%).

Conclusion: The most frequently prescribed AED in the study was Phenytoin followed by Phenobarbital and levitracetam.

I. Introduction

Epilepsy (from the Ancient Greek ἐπιληψία (epilēpsía) —to seize”) is a common chronic neurological disorder characterized by recurrent unprovoked seizures. Epilepsy is believed to affect 1% to 2% of the population; approximately 2 million people have been diagnosed with epilepsy. The incidence is highest in childhood and old age. The prognosis is good if the patient adheres strictly to prescribed treatment. Antiepileptic drug therapy is the mainstay of treatment for most patients with epilepsy. Seizure classification is an important element in designing the treatment plan, since some antiepileptic drugs have different activities against various seizure types. The International League Against Epilepsy classify the three main types of seizures: partial, generalized, and unclassified.

Amongst the various factors affecting anti-epileptic drug (AED) usage, the major determinants are type of epilepsy, age and gender of patient, side effect profile and availability of medicines, affordability of the patient, and preference of the treating physician as well as the practice setting. Attempt to control epilepsy is done using mono and poly therapy. Due to the long duration of treatment, various adverse reactions (ADRs) are seen, which require change of medication and monitoring. A recent study in Bangalore, India, reported that the problem is nearly two and half times higher in rural areas as compared to urban areas, where they are not receiving any treatment.

Begin with monotherapy about 50% to 70% of patients can be maintained on one antiepileptic drug (AED), but all are not seizure free. Up to 60% of patients with epilepsy are noncompliant, and this is the most common reason for treatment failure. Drug therapy may not be indicated in patients who have had only one seizure or those whose seizures have minimal impact on their lives. Patients who have had two or more seizures should generally be started on AEDs.

Factors favoring successful withdrawal of AEDs include a seizure-free period of 2 to 4 years, complete seizure control within 1 year of onset, an onset of seizures after age 2 years and before age 35 years, and a normal EEG.

Many controlled clinical trials have tested the efficacy of the older Anti-Epileptic Drugs (AEDs), (such as Phenobarbital and Phenytoin) and newer AEDs (such as Carbamazepine and Valproic acid) in controlling seizure frequency and their safety when prescribed in monotherapy or in combination.

The interest in drug utilization studies began in the early 1960s, and its importance has increased since then because of 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.

Purpose of the study is to investigate the use of antiepileptic drugs in epilepsy, Changes in prescription patterns, exposure of specific drugs to certain patient groups, combination of drugs, generic substitution, and potential for drug abuse and quantify the use of antiepileptic drugs (AEDs) in epilepsy and other disorders to be investigated in a tertiary care hospital

II. Background

An epileptic seizure is an episode of neurologic dysfunction in which abnormal neuronal firing is manifest clinically by changes in motor control, sensory perception, behavior, and/or autonomic function. Epilepsy is the condition of recurrent spontaneous seizures arising from aberrant electrical activity within the brain. While anyone can experience a seizure under the appropriate pathophysiological conditions, epilepsy suggests an enduring alteration of brain function that facilitates abnormal neuronal firing.

The aberrant electrical activity that underlies epilepsy is the result of biochemical processes at the cellular level promoting neuronal hyperexcitability and neuronal hypersynchrony. However, a single neuron, discharging abnormally, is insufficient to produce a clinical seizure, which occurs only in the context of large neuronal networks. Cortical and several key subcortical structures are involved in generating a seizure

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Causes

- About half of all epilepsy cases are idiopathic; possible causes of other cases include:
- Birth trauma (inadequate oxygen supply to the brain, blood incompatibility, or hemorrhage)
- Perinatal infection
- Anoxia
- Infectious diseases (meningitis, encephalitis, or brain abscess)
- Ingestion of toxins (mercury, lead, or carbon monoxide)
- Brain tumors
- Inherited disorders or degenerative disease, such as phenylketonuria or tuberous sclerosis
- Head injury or trauma
- Metabolic disorders, such as hypoglycemia and hypoparathyroidism
- Cerebrovascular accident (hemorrhage, thrombosis, or embolism).

Classification of seizure types

Seizure Type	Subtypes
Partial Seizures	Simple partial seizures Complex partial seizures Partial seizures with secondary generalization
Generalized Seizures	Absence Tonic-clonic Tonic Atonic Myoclonic
Unclassified Seizures	Neonatal seizures Infantile spasms

Pathophysiology

Some neurons in the brain may depolarize easily or be hyperexcitable; this epileptogenic focus fires more readily than normal when stimulated. In these neurons, the membrane potential at rest is less negative or inhibitory connections are missing, possibly as a result of decreased gamma-amino butyric acid (GABA) activity or localized shifts in electrolytes.

On stimulation, the epileptogenic focus fires and spreads electrical current to surrounding cells. These cells fire in turn and the impulse cascades to one side of the brain (a partial seizure), both sides of the brain (a generalized seizure), or cortical, subcortical, and brain stem areas.

The brain's metabolic demand for oxygen increases dramatically during a seizure. If this demand isn't met, hypoxia and brain damage ensue. Firing of inhibitory neurons causes the excitatory neurons to slow their firing and eventually stop. If this inhibitory action doesn't occur, the result is status epilepticus: one seizure occurring right after another and another; without treatment the anoxia is fatal.

Signs and symptoms

The hallmark of epilepsy is recurring seizures, which can be classified as partial, generalized, status epilepticus, or unclassified (some patients may be affected by more than one type).

Complications

Complications may include:

- Hypoxia or anoxia from airway occlusion
- Traumatic injury
- Brain damage
- Depression and anxiety.

Diagnosis

Clinically, the diagnosis of epilepsy is based on the occurrence of one or more seizures, and proof or the assumption that the condition that caused them is still present. Diagnostic tests that help support the findings include:

Computed tomography or magnetic resonance imaging reveal abnormalities.

Electroencephalogram (EEG) reveals paroxysmal abnormalities to confirm the diagnosis and provide evidence of the continuing tendency to have seizures. In tonic-clonic seizures, high, fast voltage spikes are present in all leads; in absence seizures, rounded spike wave complexes are diagnostic. A negative EEG doesn't rule out epilepsy, because the abnormalities occur intermittently.

Skull X-ray may show evidence of fractures or shifting of the pineal gland, bony erosion, or separated sutures.

Serum chemistry blood studies may reveal hypoglycemia, electrolyte imbalances, elevated liver enzymes, and elevated alcohol levels, providing clues to underlying conditions that increase the risk of seizure activity.

Treatment

Treatment may include: drug therapy specific to the type of seizure, including phenytoin, carbamazepine, phenobarbital, and primidone for generalized tonic-clonic seizures and complex partial seizures — I.V. fosphenytoin (Cerebyx) is an alternative to phenytoin (Dilantin) that is just as effective, with a long half-life and minimal CNS depression (stable for 120 days at room temperature and compatible with many frequently used I.V. solutions; can be administered rapidly without the adverse cardiovascular effects that occur with phenytoin) valproic acid, clonazepam, and ethosuximide for absence seizures gabapentin (Neurontin) and felbamate as other anticonvulsant drugs surgical removal of a demonstrated focal lesion, if drug therapy is ineffective surgery to remove the underlying cause, such as a tumor, abscess, or vascular problem vagus nerve stimulator implant may help reduce the incidence of focal seizure I.V. diazepam, lorazepam, phenytoin, or phenobarbital for status epilepticus administration of dextrose (when seizures are secondary to hypoglycemia) or thiamine (in chronic alcoholism or withdrawal).

Important characteristics of antiepileptic medications

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Carbamazepine	Na ⁺ channel inhibition	Partial Tonic-Clonic	Neurological: dizziness, diplopia, ataxia, vertigo Non-Neurological: aplastic anemia, leucopenia, gastrointestinal irritation, hepatotoxicity, hyponatremia, skin rash*	Enzyme Substrate: CYP 3A4, 2C8 Enzyme Inducer: CYP 1A2, 2B6, 2C8, 2C9, 2C19, 3A4 Enzyme Inhibitor: None	Yes
Clonazepam	Potentiate GABA receptor function	Absence Atypical Absence	Neurological: ataxia, sedation, lethargy Non-Neurological: anorexia	Enzyme Substrate: CYP 3A4 Enzyme inducer:	No

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		Myoclonic		None Enzyme Inhibitor: None	
Ethosuximide	T-type Ca ²⁺ channel inhibition in thalamus	Absence	Neurological: ataxia, lethargy, headache Non-Neurological: gastrointestinal irritation, skin rash, bone marrow suppression	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	Yes, Only Available in Generic
Felbamate	NMDA receptor antagonist and increase GABA availability	Partial Lennox-Gastaut	Neurological: insomnia, dizziness, sedation, headache Non-Neurological: aplastic anemia, hepatic failure, weight loss, gastrointestinal irritation	Enzyme Substrate: CYP 2E1, 3A4 Enzyme inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	No, but Patent Expired 9/26/09
Gabapentin	GABA analogue for alpha-2 delta subunit	Partial	Neurological: sedation, dizziness, ataxia, fatigue Non-Neurological: gastrointestinal irritation, weight gain, edema	Enzyme Substrate: None Enzyme Inducer: None Enzyme Inhibitor: None	Yes
Lacosamide	Na ⁺ channel inhibition	Partial	Neurological: headache, dizziness, diplopia, ataxia, fatigue, tremor, somnolence, blurred vision Non-Neurological: Nausea, vomiting, diarrhea	Enzyme Substrate: CYP 2C19 Enzyme inducer: None Enzyme Inhibitor: CYP 2C19	No
Lamotrigine	Decrease glutamate release	Partial Tonic-Clonic Atypical Absence Myoclonic Lennox-Gastaut	Neurological: dizziness, diplopia, sedation, ataxia, headache Non-Neurological: skin rash*	Enzyme Substrate: UGT1A4 Enzyme inducer: None Enzyme Inhibitor: None	Yes
Levetiracetam	Synaptic vesicle release modulation	Partial	Neurological: sedation, fatigue, incoordination, psychosis Non-Neurological: anemia, leucopenia	Enzyme Substrate: None Enzyme inducer: None Enzyme Inhibitor: None	Yes
Oxcarbazepine	Na ⁺ channel inhibition	Partial	Neurological: fatigue, ataxia, dizziness, diplopia Non-Neurological: aplastic anemia, leucopenia, gastrointestinal irritation, hepatotoxicity, hyponatremia, skin rash	Enzyme Substrate: CYP Enzyme Inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	Yes
Phenobarbital	Potentiate GABA receptor function	Partial Tonic-Clonic	Neurological: sedation, ataxia, confusion, dizziness, decreased libido, depression Non-Neurological: Skin rash, hepatotoxicity	Enzyme Substrate: CYP 2C9, 2C19, 2E1 Enzyme Inducer: CYP 1A2, 2A6, 2B6, 2C8, 2C9, 3A4 Enzyme Inhibitor: None	Yes, Only Available in Generic
Phenytoin	Na ⁺ and Ca ²⁺ channel inhibition	Partial Tonic-Clonic	Neurological: dizziness, diplopia, ataxia, confusion Non-Neurological: gingival hyperplasia, peripheral neuropathy, lymphadenopathy, hirsutism, osteomalacia, hepatotoxicity, facial coarsening, skin rash*	Enzyme Substrate: CYP 2C9, 2C19, 3A4 Enzyme Inducer: CYP 2B6, 2C8, 2C9, 2C19, 3A4 and UDPGT Enzyme Inhibitor: None	Yes
Pregabalin	GABA analogue for alpha-2 delta subunit	Partial	Neurological: ataxia, somnolence, dizziness, blurred vision, diplopia Non-Neurological: peripheral edema, increased appetite	Enzyme Substrate: None Enzyme Inducer: None	No

				Enzyme Inhibitor: None	
Primidone	Inhibition of neuronal firing	Partial Tonic-Clonic	Neurological: sedation, ataxia, confusion, dizziness, decreased libido, depression Non-Neurological: Skin rash	Enzyme Substrate: None Enzyme inducer: CYP 1A2, 2B6, 2C8, 2C9, 3A4 Enzyme Inhibitor: None	Yes
Rufinamide	Na ⁺ channel inhibition	Lennox-Gastaut	Neurological: headache, dizziness, fatigue, somnolence, convulsion, diplopia, tremor, nystagmus Non-Neurological: nausea, vomiting, nasopharyngitis, blurred vision	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	No
Tiagabine	Increase GABA availability	Partial Tonic-Clonic	Neurological: confusion, sedation, depression, speech problems, paresthesias, psychosis Non-Neurological: gastrointestinal irritation	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	No
Topiramate	Na ⁺ channel inhibition	Partial Tonic-Clonic Lennox-Gastaut	Neurological: psychomotor slowing, sedation, speech problems, fatigue, paresthesias Non-Neurological: kidney stones, glaucoma, weight loss, hypohydrosis	Enzyme Substrate: None Enzyme inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	Yes
Valproic Acid	T-type Ca ⁺⁺ channel inhibition in thalamus increase GABA availability	Partial Tonic-Clonic Absence Atypical Absence Myoclonic	Neurological: ataxia, sedation, tremor Non-Neurological: Hepatotoxicity, thrombocytopenia, gastrointestinal irritation, weight gain, hyperammonemia	Enzyme Substrate: UGT 1A6, 1A9, 2B7, beta-oxidation Enzyme Inducer: CYP 2A6 Enzyme Inhibitor: CYP 2C9, 2C19, 2D6, 3A4	Yes
Vigabatrin	Analog of GABA, inhibits GABA catabolism	Complex Partial	Neurological: headache, fatigue, drowsiness, dizziness, tremor, agitation, visual field defects, abnormal vision, diplopia Non-Neurological: nausea, vomiting, diarrhea, weight gain, skin rash	Enzyme Substrate: None Enzyme inducer: None Enzyme Inhibitor: None	No
Zonisamide	Na ⁺ channel inhibition	Partial	Neurological: sedation, dizziness, confusion, headache, psychosis Non-Neurological: Anorexia, renal stones, hypohydrosis	Enzyme Substrate: CYP 2C19, 3A4 Enzyme Inducer: None Enzyme Inhibitor: None	Yes

**Legend: Ca²⁺ = calcium ion, CYP = cytochrome P enzyme, GABA = gamma amino butyric acid, Na⁺ = sodium ion, NMDA= N-methyl D-aspartic acid.
* denotes skin rash risk (Steven's Johnson syndrome and Toxic Epidermal Necrolysis) related to Human Leukocyte Antigen (HLA)-phenotype.**

Over the last decade newer antiepileptic drugs that have been approved for use by the Food and Drug Administration (FDA) in the treatment of epilepsy. While most newer antiepileptic drugs are approved as second line agents for the treatment of refractory seizures, topiramate, oxcarbazepine and lamotrigine are also approved for monotherapy in certain situations.

III. Methodology

Study Site: This study is being conducted at Fortis Escorts hospital, Amritsar. It is a Tertiary Care Superspeciality Hospital.

Study Design: This was a hospital based observational study conducted on in-patients to review the current prescribing pattern of antiepileptic drugs in patients with epilepsy admitted to medicine wards.

Sample Size: A total of 35 In-patients from different units of medicine department, who were on AEDs and fulfilled the inclusion criteria were selected and the rest of the patients were excluded from the study, and the data were collected in a well designed proforma.

Study period: The observational study was conducted for one month.

Study Criteria:

- **Inclusion Criteria:** All In-patients who were treated with AEDs admitted in different units of Medicine Department.
- **Exclusion Criteria:** All pregnant women who are on AEDs.

Source of Data: Data was collected using a well-designed patient data collection form.

- By reviewing the patient's treatment chart, case sheets of the patients.
- From the Medical Record Department.

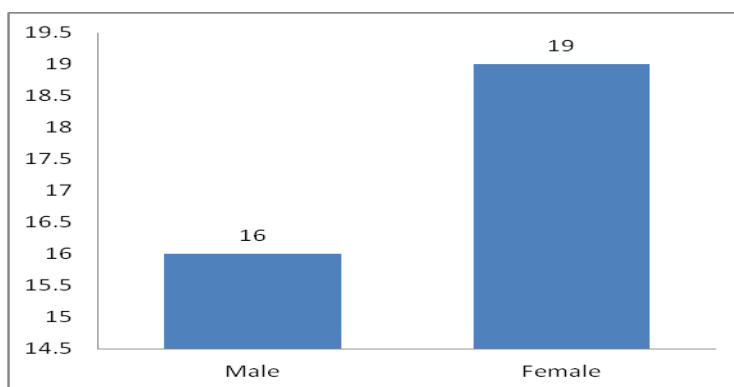
Preparation of data collection form: Information extracted from the case files will include: Demographic data ,If he/she is a known case of epilepsy and diagnosis (provisional or confirmatory). Treatment: AEDs prescribed and prescription of the AEDs by generic names. The recommended dosages of the AEDs were obtained from the patient case files and discharge summary Drugs which reduce seizure threshold.

Statistical method.

The data of each case file was collected and analyzed by a Suitable method.

IV. Results & Interpretation

Gender

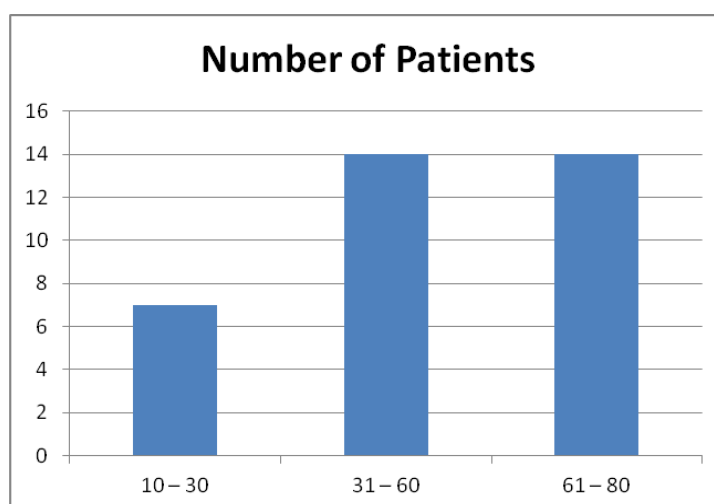


Interpretation

After study on the epileptic patients, following data were collected:

- Total no. patients: 35
- Total no. of male:16
- Total no. of female:19

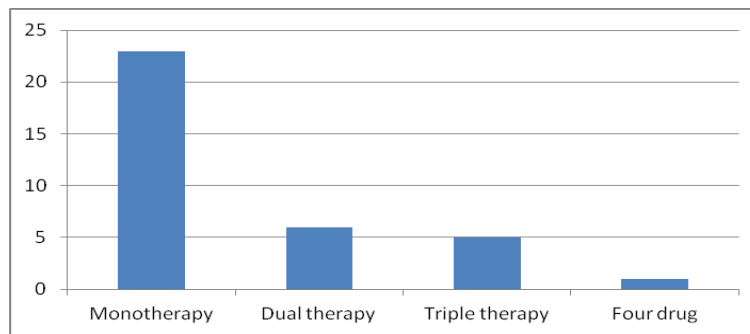
Age



Interpretation

- Total no of patients that come under the age group 10-30 is 7
- Total no of patients that come under the age group 31-60 is 14
- Total no of patients that come under the age group 61-90 is 14

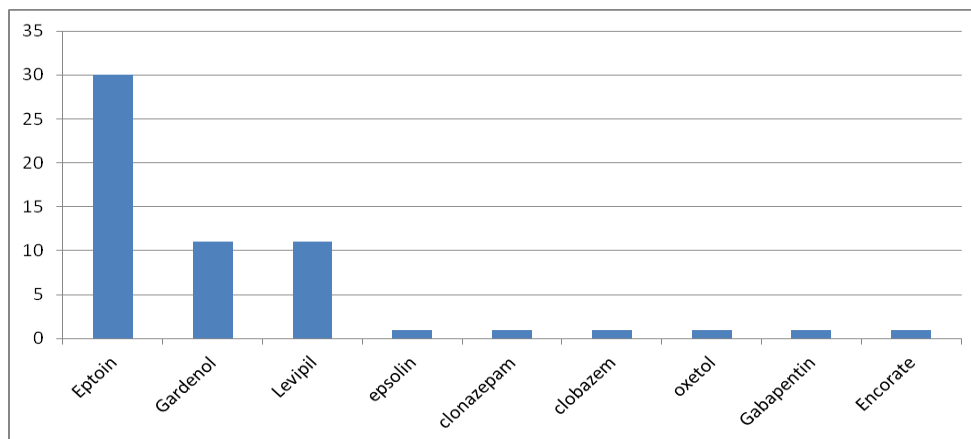
Type of Therapy



Interpretation

- Mono therapy is prescribed in 23 patients.
- Dual therapy is prescribed in 6 patients.
- Triple therapy is prescribed in 5 patients.
- Four drugs are prescribed in 1 patient.

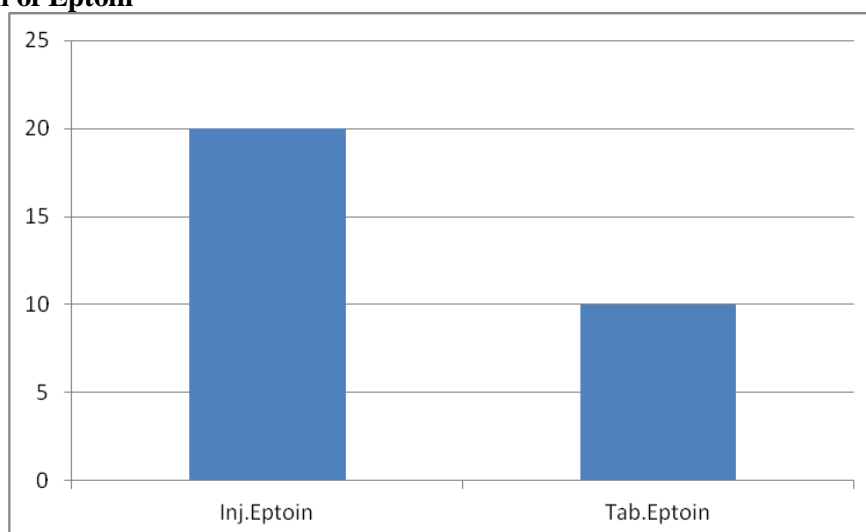
Drugs



Interpretation

Most commonly prescribed drug concluded is phenytoin which accounts for 30 (85.30%) in both the genders, followed by phenobarbitone 11 (31.18%) and levitracetam usage was 11 (31.18%).

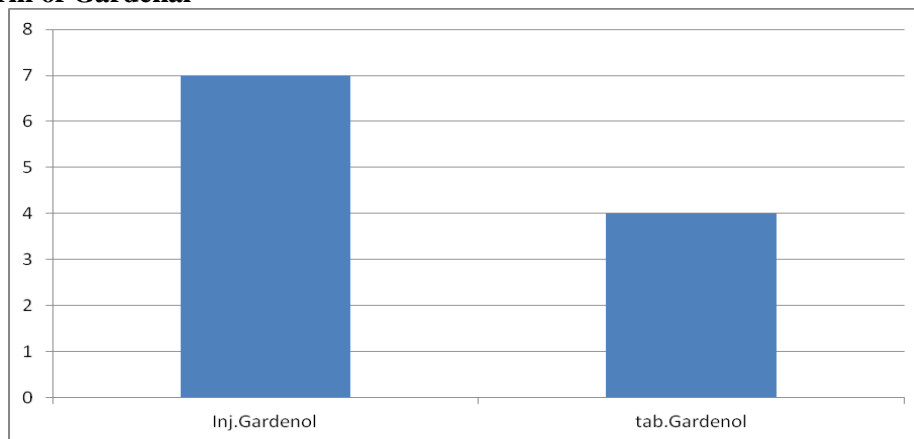
Dosage Form of Eptoin



Interpretation

- Inj.Eptoin are given in 20 patients
- Tab.Eptoin are given in 10 patients

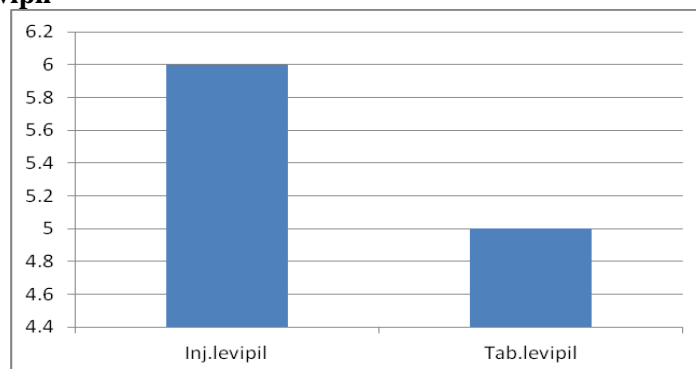
Dosage Form of Gardenal



Interpretation

- Inj.Gardenol is given in 7 patients
- Tab.Gardenol is given in 4 patient

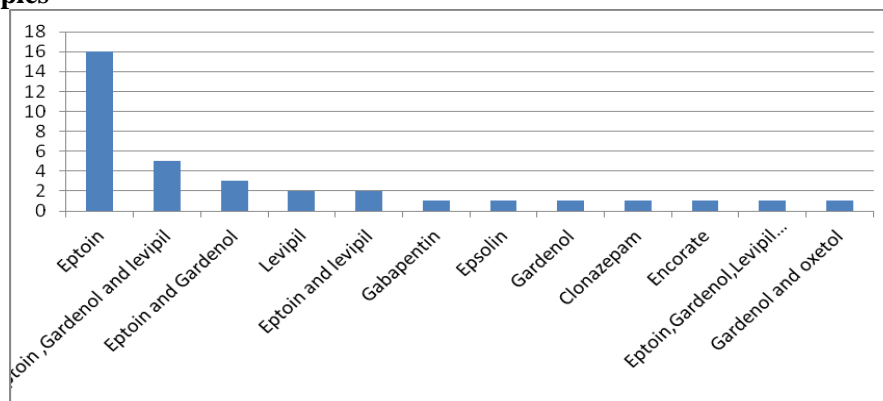
Dosage Form of Levipil



Interpretation

- Inj.levipil is given in 6 patients
- Tab.levipil is given in 5 patients

Drug Therapies



Interpretation

- In Mono Therapy, Eptoin has been in most cases.
- In Dual Therapy, Eptoin & Gardenol has been given in most cases.
- In Triple Therapy, Eptoin, Gardenal & Levipil has been given in most cases.
- The 4 drug combination has been given to only 1 patient and the drugs are Eptoin, Gardenal, Levipil, and Clobazam.

V. Discussion

- The beneficial effects of second generation drugs can also be studied conduction Drug utilization studies in this area.
- A total of 35 epileptic patients were included.
- The incidence of epilepsy was found to be higher in female than in males and also the incidence of epilepsy increases with an increase in age.
- Another finding observed in the study was that Phenytoin was the most frequently prescribed drug followed by Phenobarbital and levitracetam.
- The above studies justified the use of Phenytoin because it was the equally effective as other AEDs when used in monotherapy, very less incidences of adverse drug reactions (ADR) and also the cost was least

VI. Conclusion

- Monotherapy is the type of therapy most frequently used in all types of seizures.
- The selection of AEDs is based on efficacy for specific seizure types and epileptic syndromes.
- Most commonly prescribed drug concluded by our study is Phenytoin followed by Phenobarbitone and Levitracetam usage.
- The percentage of female suffering from epilepsy was higher than males.
- The study shows that most of the patients were from the age group of 60-70 years.

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