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RESEARCH ARTICLE

A Prospective Observational Study on Changing Trends of Antiepileptics Prescription Amongst Physicians in India

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ABSTRACT
Epilepsy is one of the common neurological disease affecting millions of people worldwide. Multiple class of antiepileptic drugs (AEDs) are available which makes it difficult to select an appropriate drug therapy for epilepsy. With introduction of newer generation of antiepileptics, the drug Pool has become wider. Factors which determine the selection of therapy includes seizure type, adverse effect, drug-drug interaction, age, pregnancy, cost of treatment and drug compliance. Though the older generation of antiepileptics were effective in controlling seizures, we found that newer generation of antiepileptics are gaining popularity among the prescriber. Reason for this shift being, better efficacy, fewer side effect and better compliance by the patients. We completed the study with the conclusion that newer antiepileptic especially levetiracetam, are more preferred by doctors in comparison with older antiepileptic drugs for control of seizures, though previous generation of antiepileptics has still role in management of epilepsy and individualistic approach is needed in choosing appropriate antiepileptics.

Key words: Epilepsy, Standard Antiepileptic, Compliance,

1. INTRODUCTION

Epilepsy is a common neurological disorder manifesting with recurrent seizures[1]. It affects over 70 million people worldwide[2]. Over the last 20 years, use of antiepileptic drugs for epilepsy has improved significantly[3].

As newer antiepileptic drugs are introduced, the selection of the right therapy has become more complex. An individual approach is required in the selection of an antiepileptic drug. The selection of suitable antiepileptic drugs for the management of epilepsy is key for adequate control of disease, and various factors which influence the choice of drugs includes; efficacy, adverse effects, drug-drug interactions, age, pregnancy, cost of treatment, and compliance by the patient. The rightful consideration will reduce the possibility of treatment failure and improves patient's quality of life. Special consideration must be given to women of childbearing age, pediatric patients, and geriatric patients.[4-6.]

Medical management of epilepsy either with polytherapy or monotherapy is very debatable. Prior to the development of modern antiepileptic drugs polytherapy was generally favoured. In the 20th century, the standard antiepileptic drugs (first generation) carbamazepine, phenobarbitone, valproate, phenytoin, and ethosuximide were often used in polytherapy. However, several studies suggested that monotherapy is an optimal approach for reducing seizure frequency and severity, as it generally lowers the risk of side effects and drug interactions and is more acceptable. Although polytherapy is still required in some cases. Polytherapy with a combination of greater than or equal to three antiepileptic drugs was associated with higher adverse effects and lower seizure control as compared to monotherapy and combination of two antiepileptic drugs.[7,8]

Epilepsy prescription patterns have been altered by new generation antiepileptic drugs.[9]In recent years, several newer antiepileptic drugs have been introduced: levetiracetam, topiramate, zonisamide, lamotrigine, tiagabine, vigabatrin, felbamate, perampanel, pregabalin, brivaracetam, lacosamide. Some of these drugs have superior action, fewer adverse effects, less drug interaction, and lower teratogenicity; they are often used in patients with drug-resistant epilepsy to older agents in up to 40% to 50% of patients. Older generation drugs are still being used as first line management, despite increasing use of newer generation drugs.

Few of New-generation drugs are not found to be superior comparing to older-generation drugs for patients with newly diagnosed epilepsy, but have proven efficacy and are used as an add-on therapy.[10-14] These new drugs have improved seizure control and are better tolerated when used as adjunctive therapy.[15]

Levetiracetam is a new antiepileptic drug marketed since 2000. It is approved by FDA as adjunctive therapy for partial seizures and primary generalized tonic-clonic seizures. However off label Levetiracetam is emerging as a first-line treatment for the management of epilepsy, and is being chosen as an alternative first-line treatment option for partial and generalized tonic-clonic seizures (GTCS) 16,[17.] The pharmacokinetic profile of levetiracetam including rapid achieving steady-state concentration ,good oral bioavailability, and minimal first pass metabolism[18]also makes it as a preferred drug.

we planned this study to find what's are the preferred drugs among physicians for treatment of epilepsy and if there is any drift towards newer antiepileptic in their prescription and the reason for the same.

2. AIM AND OBJECTIVES

- To understand the changing trend of prescription of antiepileptic drugs
- To identify which AEDs are most prescribed to adults, pregnant women, geriatric patients, and pediatric patients of GTCS and partial seizures.
- To evaluate why newer drugs are most used.

3. MATERIALS AND METHODS

This study was prospective and observational in design. The study has a major aspect of trying to understand and analyze the changing use of antiepileptic drugs among doctors.

Study site

Neurosciences Department

Study design

Prospective and Observational study

Sample size

The sample has been collected by using simple random sampling method. The minimum sample size is 95 on assumption of 95% level of significance(z=1.96), 80% power of the study,10% of precision and 55% expected proportion of valproic acid.[9]After 5% adjustment of loss information due to any technical failure, so the final sample size will be 100. The 100 Sample is comprised of Neurosurgeons and Neurologists who had willingly to take part in the study.

Statistical analysis

The collected data has been summarized in form of frequencies and percentage. The qualitative

variables have been summarized using descriptive statistics such as minimum value, maximum value and modal value.

Data collection tool

Questionnaire sent in person or online.

Inclusion Criteria

Neurologist and neurosurgeons, who are managing averagely 10 or more seizure patients per month in their outpatient department.

Exclusion Criteria

Physicians who don't meet the minimum criteria of patient load in their outpatient department.

All the data pertaining to the study was collected and recorded through a specially designed questionnaire form that was provided to the neurosurgeon and neuro-physicians via mail and in person. In total, 100 responses were collected, including both neurosurgeons and neuro-physicians. he questionnaire has a definite set of questions regarding their preferred current line of treatment, use of newer AEDs, preferred antiepileptic drugs in pregnant women, observed side effects of older AEDs, and any shift in fist line antiepileptic drugs prescription and the reasons for the same. The question pattern was multiple choice, and space was provided for the comments. More than one response was also allowed depending upon the question with mentioning of their priority. Responses are collected from both government and private hospitals all over India.

Data collected from questions was analysed and bifurcated by drug used in GTCS and partial seizure. Change in trend of antiepileptic drugs was evaluated. Graphs were drawn from the data and results were concluded.

4. RESULT

There are 37% neurologist and 63 % neurosurgeon out of 100 responses.

Generalized tonic-clonic seizures (GTCS) (69%) were found to be the most common seizure type in the clinical practice of 100 physicians.

Table 1: - Type of Seizures

Type of seizure	Percentage
Generalized tonic clonic seizure	69%
Partial seizure	27%
Complex partial seizure	4%

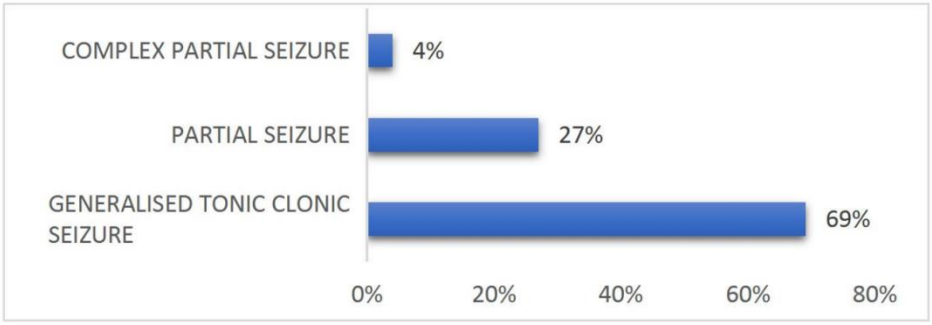

Fig.1: -Types of seizures

According to our study, the newer generation of antiepileptic medications were perceived better by physicians in controlling seizures.

Table 2: - Generation better in controlling seizures (total percentage is out of 100%)

Generation better in controlling seizures	Percentage
Older	38.4
Newer	61.6

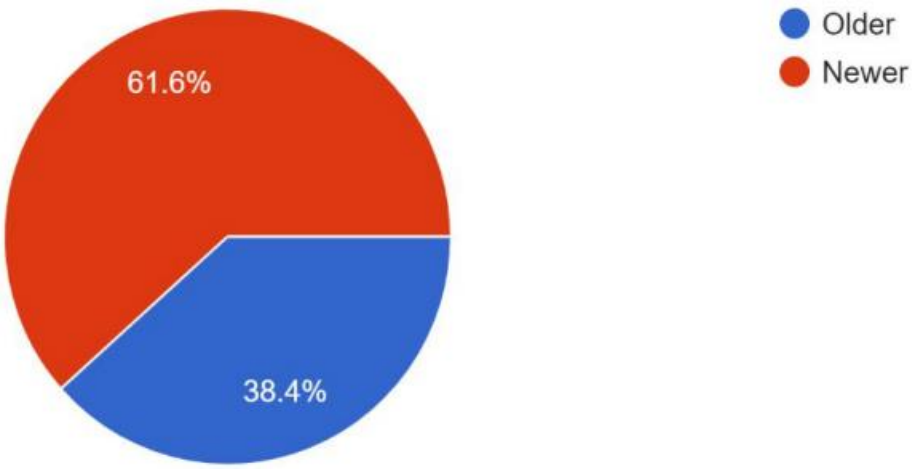

Fig. 2: - Generation better in controlling seizures

The selection of antiepileptic medication for patients with epilepsy depends on various primary factors, and drug efficacy is the most common primary factor considered by physicians while prescribing antiepileptic medication.

Table 3: - Factors deciding for choice of AEDs (each percentage is out of 100%)

Factors deciding for choice of AEDs	**Percentage**
Drug efficacy	76%
Compliance	63%
Side effects	57%
Tolerability	51%

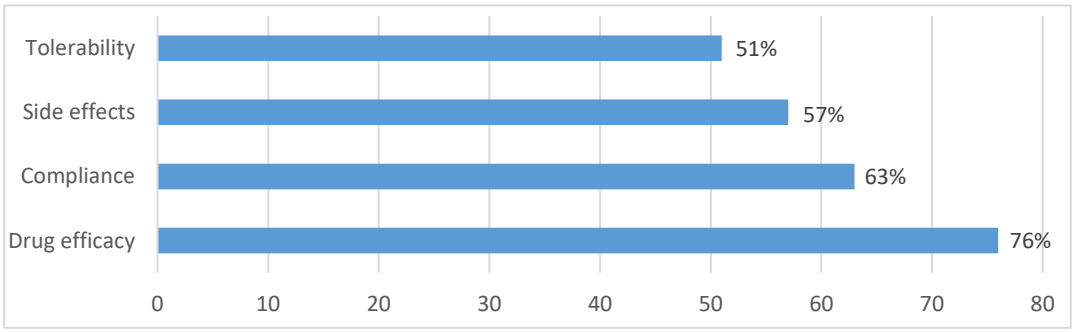

Fig. 3: -Factors deciding for choice of AEDs

Out of 100 responses collected, 67% physicians have altered their prescription pattern in the past two years or more.

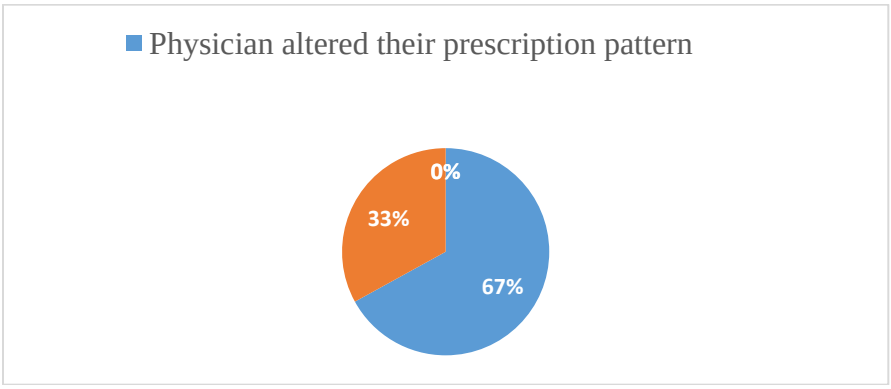

Fig. 4: - Number of physicians altered their prescription pattern

Patient's compliance, closely followed by lesser side effects, is the most significant factor of change in the antiepileptic drug prescription pattern for GTCS and partial seizure.

Table 4: - Reasons for the change in prescription pattern (each percentage is out of 100%)

Reason for the change in prescription pattern	**Percentage**
Patient compliance is better	82% (78 count of response)
Lesser side effects	75% (72)
Newer ones are more efficacious	33% (31)
Financially more affordable	21% (20)

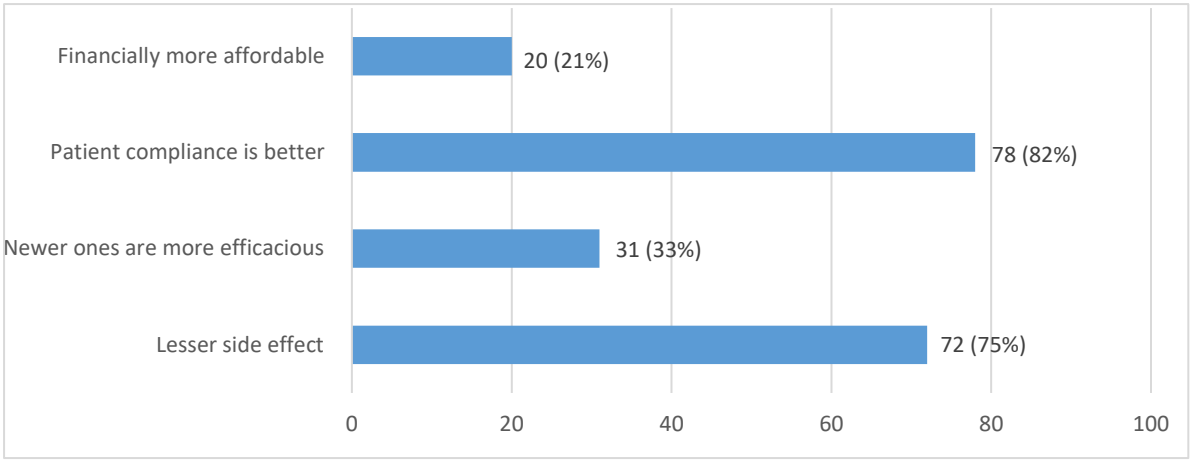

Fig. 5: - Reasons for the change in prescription pattern

Earlier valproic acid (76%) followed by phenytoin with 70%, were the most prescribed antiepileptic drugs by physicians for control of GTCS.

Table 5: - Older generation antiepileptic drugs for GTCS (each drug percentage is out of 100%)

Previously used antiepileptic drugs for GTCS	**Percentage**
Valproic acid	76%
Phenytoin	70%
Carbamazepine	32%
Phenobarbitone	24%

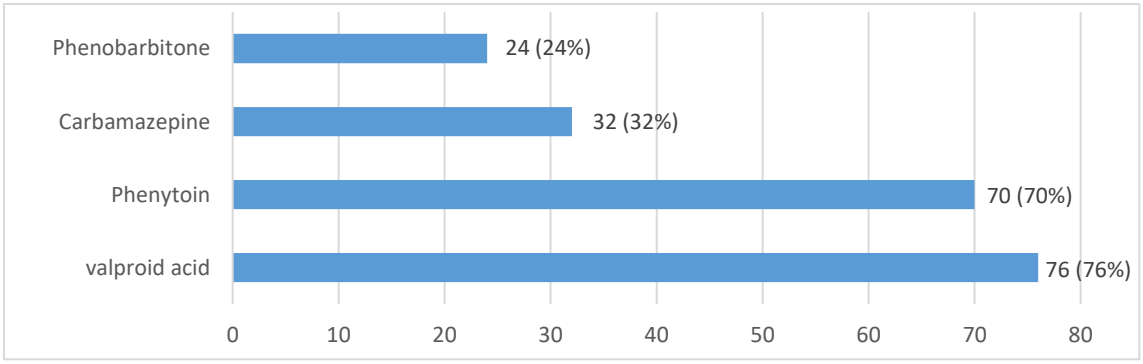

Fig. 6: -Previously used antiepileptic drugs for GTCS from first generation

According to are study, 61% of physicians (out of 100%) have changed or altered their previously using antiepileptic drugs for ***GTCS.***

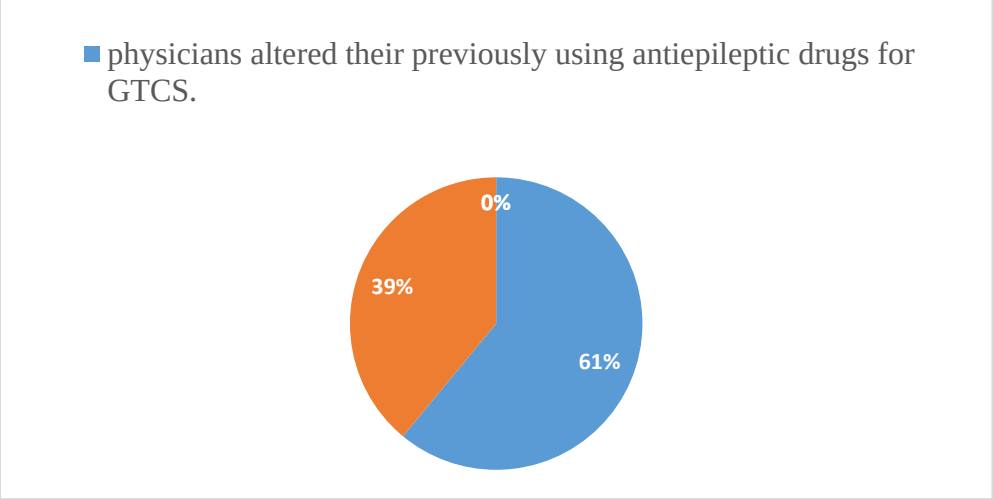

Fig. 7: - Number of physicians altered their previously using antiepileptic drugs for GTCS.

As per our research, there is slight shift towards use of newer antiepileptic like levetiracetam and lacosamide equally followed by brivaracetam.

***Table 6:* - Currently preferred antiepileptic drug for GTCS** (each drug percentage is out of 100%)

Currently preferred antiepileptic drug for GTCS	**Percentage**
levetiracetam	89%
Lacosamide	66%
Brivaracetam	63%
Topiramate	15%
Valproic acid	44%
Phenytoin	34%
Phenobarbitone	14%

Valproic acid and phenytoin are still preferred by few physicians, though their number has decreased.

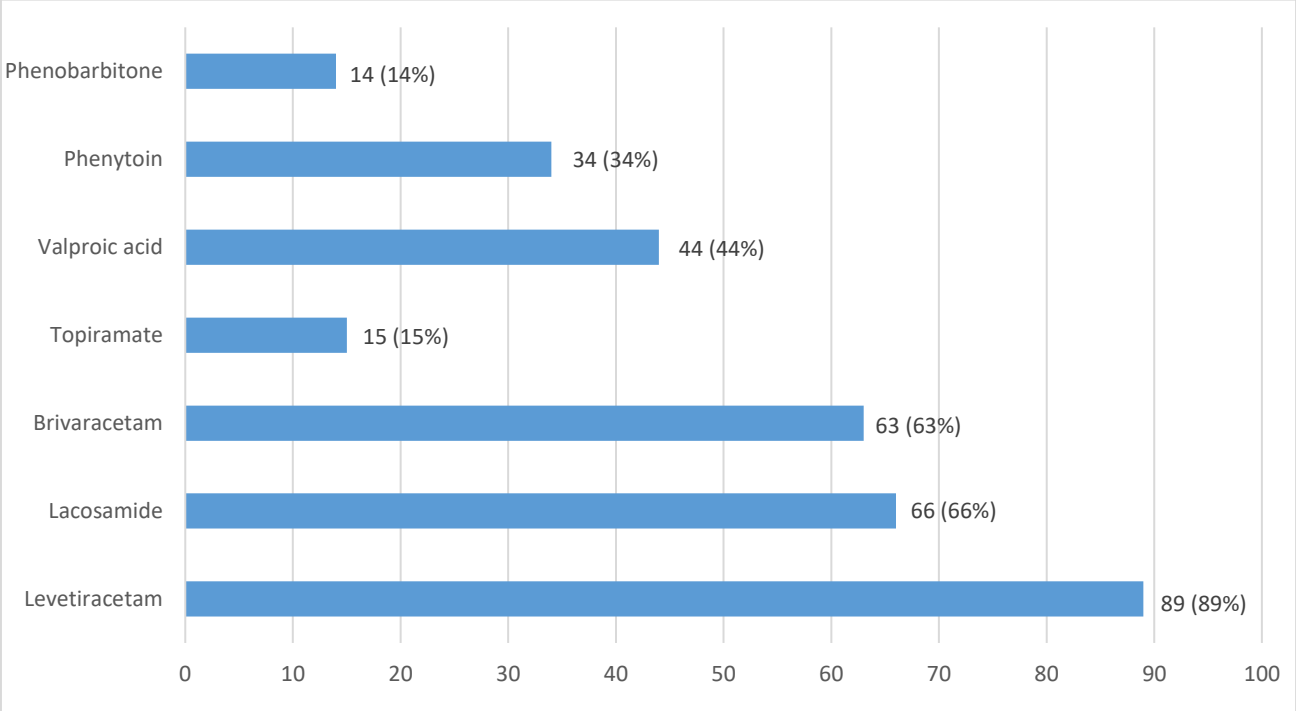

***Fig. 8:-* Currently preferred antiepileptic drug for GTCS**

For addon therapy for GTCS levetiracetam is slightly more preferred by physicians in comparison with valproic acid and phenytoin.

***Table 7:* - Preferred antiepileptic for addon therapy for GTCS** (total percentage is 100%)

Preferred antiepileptic for addon therapy for GTCS	**Percentage**
Valproic acid	20%
Phenytoin	19%
Clobazam	6%
levetiracetam	35%
Lacosamide	10%
Topiramate	5%
Perampanel	3%
Brivaracetam	2%

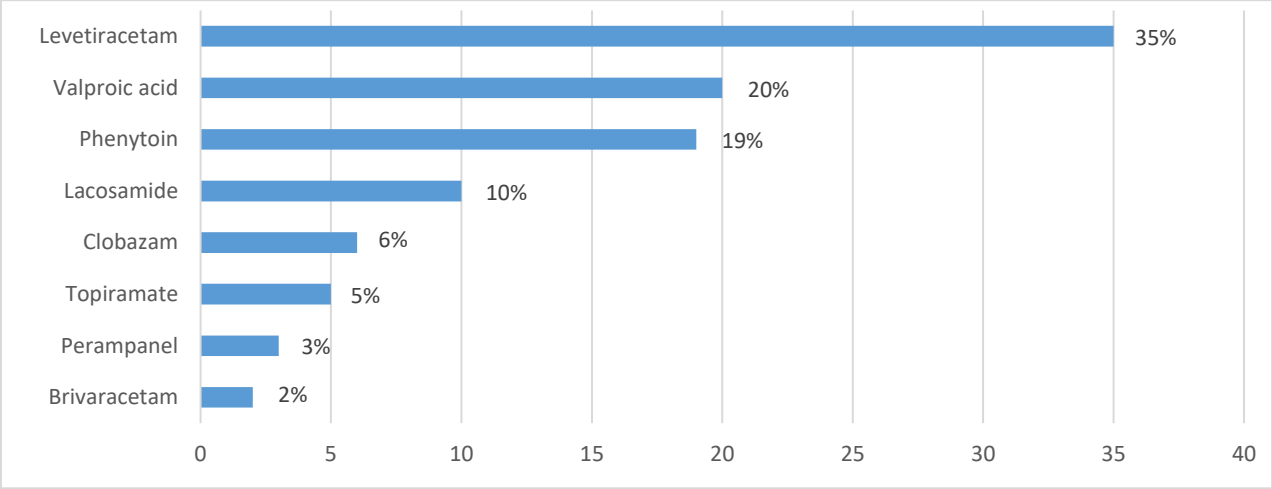

***Fig. 9:* -Preferred antiepileptic for addon therapy for GTCS**

Valproic acid still most preferred antiepileptic for partial seizures, while there is a growing preference for levetiracetam along with carbamazepine and phenytoin.

Table 8:* - *Currently preferred* antiepileptic drug *for partial seizures (each drug percentage is out of 100%)

Currently preferred antiepileptic drug for partial seizures	**Percentage**
Valproic acid	69%
Levetiracetam	60%
Phenytoin	57%
Carbamazepine	30%
Topiramate	13%
Gabapentin	11%

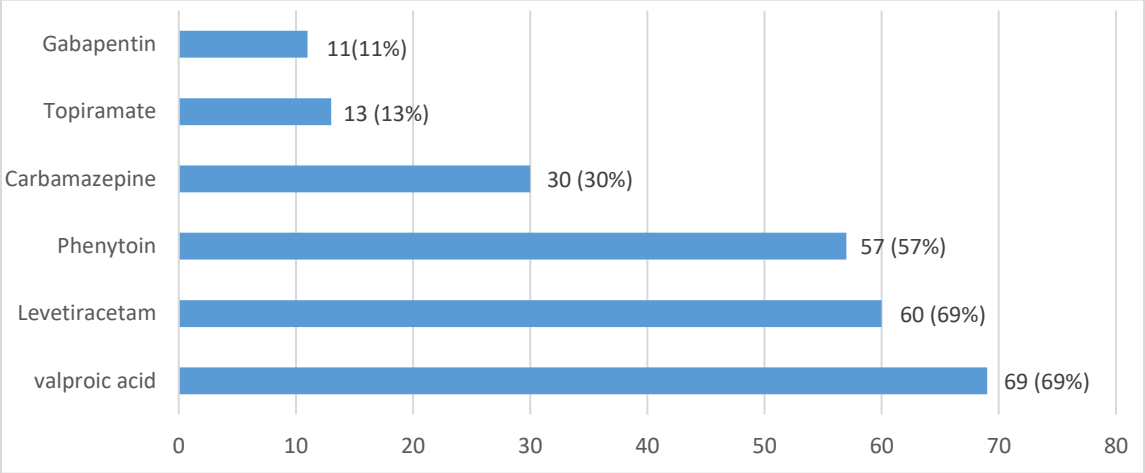

Fig. 10:- Currently preferred* antiepileptic drug *for partial seizures

According to are research, levetiracetam is the most preferred antiepileptic drug for addon therapy for partial seizure. In comparison with older antiepileptic drugs, vast numbers of physicians recommend levetiracetam.

***Table 9:* - Preferred antiepileptic for addon therapy for partial seizure**(each drug percentage is out of 100%)

Preferred antiepileptic for addon therapy for partial seizure	**Percentage**
Levetiracetam	73%
Valproic acid	10%
Lacosamide	10%
Topiramate	8%
Gabapentin	8%
Clobazam	7%
Phenytoin	4%
Brivaracetam	2%
Zonisamide	1%

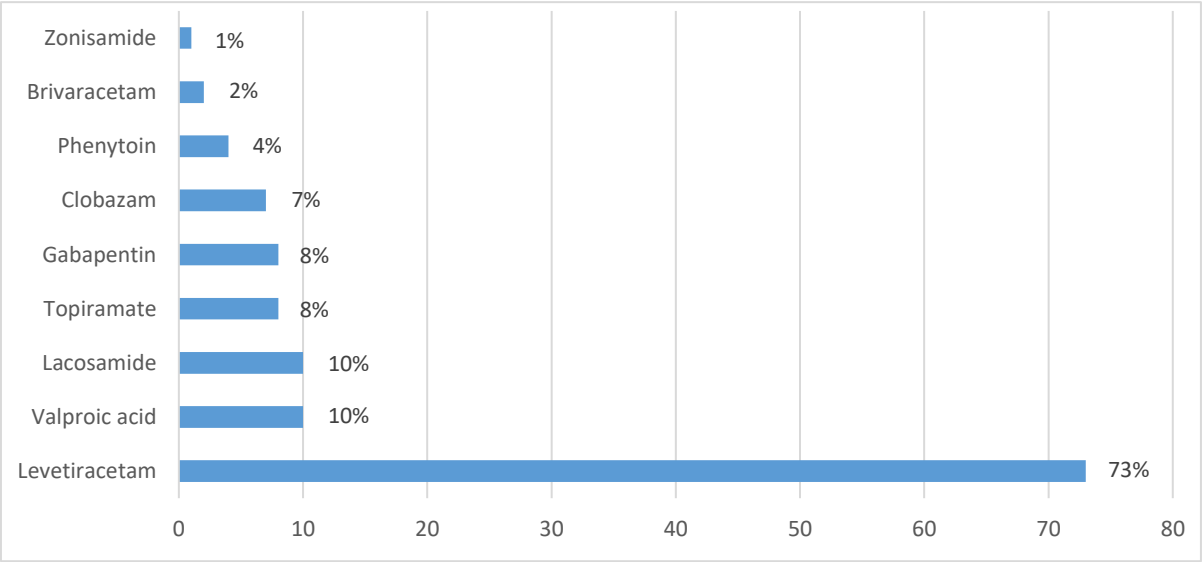

Fig. 11:- Drug used for add-on therapy for partial seizures

The preferred first-line antiepileptic drugs for woman of childbearing age and girls is Levetiracetam.

Table 10:- Preferred first line antiepileptic drugs for woman of childbearing age(each percentage is out of 100%)

Preferred first line antiepileptic drugs for woman of childbearing age	Percentage
Levetiracetam	98%
Lamotrigine	23%
Topiramate	16%
Others	2%

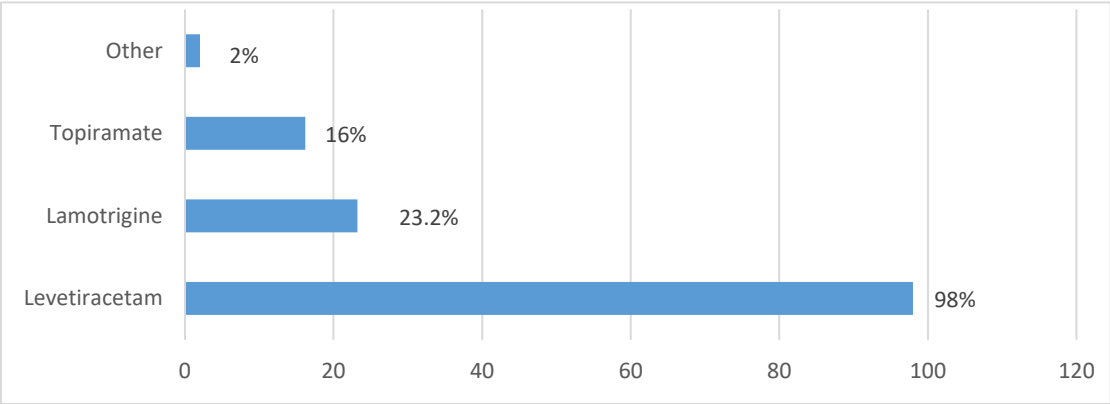

***Fig. 12:*-Preferred first line antiepileptic drugs for woman of childbearing age**

For obese patient levetiracetam is the most recommend drug followed by phenytoin.

Table 11:- Preferred Antiepileptic drugs for obese patients with GTCS

Preferred Antiepileptic drugs obese patient with GTCS	Percentage
Levetiracetam	55%
Phenytoin	28%
Lacosamide	5%
Topiramate	3%
Brivaracetam	1%
Perampanel	1%
Phenobarbitone	1%

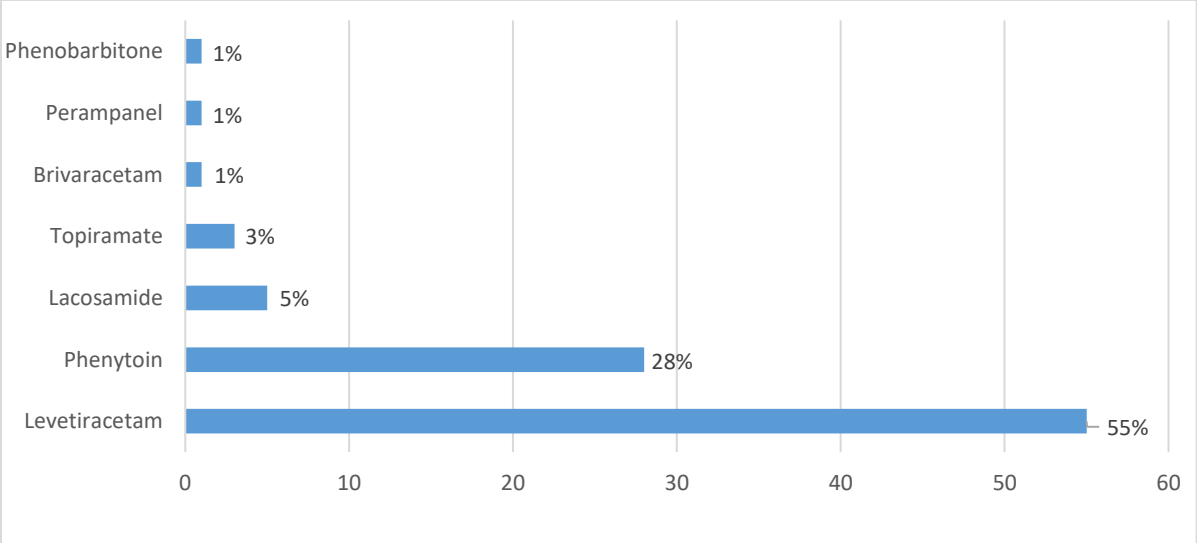

***Fig. 13:* -Preferred Antiepileptic drugs obese patient with GTCS**

Safe in woman of childbearing age and good efficacy are the perceived advantages of using levetiracetam over other antiepileptic drugs for GTCS and partial seizure.

Table 12: - Advantages of Using Levetiracetam (each percentage is out of 100%)

Advantages of Using Levetiracetam	Percentage
Safe in woman of childbearing age	90%
Good efficacy and tolerability	88%
Low rate of drug interaction	43%
Few side effects	40%

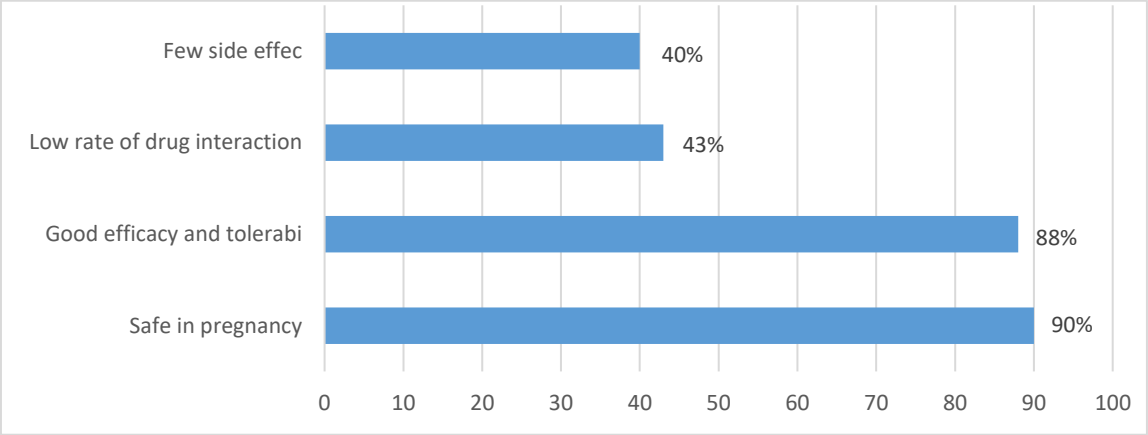

Fig. 14: -Advantages of Using Levetiracetam in Generalized & Focal seizure

5. DISCUSSION

In our study, we found that Generalized tonic clonic seizure(69%), and Partial seizure(27%) is the most common seizure type and is in comparison with the study conducted by Jawaid.W,[19] which reported that most common type of seizure was GTCS, found in(73.0%) patients (total 996 patients).

There was a change in the use of the antiepileptic drugs prescribed to patients in past few years, as the primary purpose of this study was to understand the changing trends of doctor from conventional AEDs (older AEDs) to newer AEDs, according to this study Newer generation (61.6%) antiepileptic drugs (older generation antiepileptic drugs(38.4%) are better in controlling seizures. Earlier research done by French JA,[20] concluded that new AEDs may be better tolerated than the standard older generation AEDs, newer generation AEDs has both improved tolerability and safety compared with older agents.

There are various factors which affect the treatment of patients and selection of medication. The major primary factors deciding for choice of antiepileptics medication for patients are Drug efficacy (76%), Compliance (63%), Side effects (57%), Tolerability(51%). This can be compared with a study by Mattson RH,[21] Antiepileptic drug selection is based on efficacy of medication and minimal adverse effects for patients.

Prescription patterns for antiepileptic drugs have been changed. Reason for change in prescription pattern is Better Patient compliance (82%), Lesser side effect(75%), and more efficacious(32%).This can be compared to study conducted by Vidaurre J,[22] which reported that third generation antiepileptics drugs offer new mechanisms, decreasing the occurrence of side effects and drug- drug interaction.

This study indicated that Sodium valproic acid (76%), Phenytoin (70%) were the previously used antiepileptic drug for GTCS by neurologist and neurosurgeon, though the preference is shifting towards newer generation of antiepileptics, currently valproic acid is used by 44% and phenytoin by 34% of doctors in our study. This can be compared to a study conducted by Mattson RH[23] for generalized epilepsy with tonic- clonic, absence and myoclonic seizures, the drug of choice is sodium valproate; if sodium valproate cannot be prescribed, Carbamazepine, Phenobarbital, Phenytoin may be prescribed.

There is a increased use of Levetiracetam(89%),Lacosamide(66%) and Brivaracetam(63%) as a currently preferred antiepileptic medications by the neurologists and neurosurgeons for the treatment of GTCS. Levetiracetam(35%), Valproicacid(20%),Phenytoin(19%),Lacosamide(10%), Clobazam(6%), Topiramate(5%), Perampanel(3%), Brivaracetam(2%) are

preferred antiepileptic for add-on therapy for GTCS. This study can be compared with the study conducted by Vidaurre J[24] that Brivaracetam which is a broad-spectrum antiepileptic drug, is a good choice for generalized tonic-clonic seizures and is well tolerated. Levetiracetam can be an alternative first-choicedrug. Topiramate and Lacosamide are also effective as a first choice, according to the study done by CoppolaG.[25]

This current study reports that Sodium valproic acid (69%), Levetiracetam (60%), Phenytoin (57%), Carbamazepine(30%) are widely prescribed by neurologists and neurosurgeons as the currently preferred antiepileptic medication for the treatment of partial epilepsy. This contrasts with study done by Mattson RH,[26] Drugs of first choice for partial epilepsy are Carbamazepine and Phenytoin and Valproate.

There is a trend for increase prescription of levetiracetam (73%) as add-on therapy for GTCS and partial seizure along with Valproic acid (10%), Lacosamide (10%), Topiramate (8%) are also used in addon therapy for partial seizures by neurologist and neurosurgeon. Our study gets different results in comparisons to the study conducted byElgra CE,[27] where Pregabalin administered, was highly effective and generally tolerated as add-on therapy for partial seizures.

There was substantial difference in antiepileptic drug utilization in women of childbearing age according to the study Levetiracetam (98%), Lamotrigine(23%), Topiramate(16%)are the preferred first-line antiepileptic drugs for women of childbearing age. It gets a similar result as compared to the study done by Meador KJ,[28] The most common antiepileptic drugs were Lamotrigine or Levetiracetam.

Levetiracetam (55%) and phenytoin (28%) are the choice of antiepileptic drugs for the treatment of patient with obesity, Sodium valproate use in obsess patients with GTCS may associate with weight gain. This can be compared with study done by BitonV[29] that Lamotrigine, Levetiracetam and phenytoin are weight neutral and most appropriate therapeutic choice. Drugs such as Valproate and Carbamazepine increase weight other drug such as Topiramate and decrease weight.

Use of levetiracetam in GTCS and partial have been increased, it is associated with its preferred advantages as this study reported some of the preferred advantage of levetiracetam for its use in patient with generalized and focal seizures, are Safe in pregnancy(90%), Good efficacy and Tolerability(88%), Low rate of drug interaction(43%), Few side effects(40%), in comparison with the study done by Ben Menachem E,[30] Levetiracetam is a safe and has good tolerability with rapid and complete absorption, low drug interaction and side effect.

6. CONCLUSION

The present study indicates a definitive change in trend of antiepileptic drug usage by neurologists and neurosurgeons. There is a gradual shift from older AEDs to newer AEDs; this shift or change in prescription patterns is due to better patient compliance, fewer side effects, and improved efficacy of newer AEDs. Levetiracetam is most prescribed as a newer AED for GTCS and focal seizures due to its preferred advantages, like being safe in pregnancy, having good efficacy and tolerability, low drug interactions and few side effects. Levetiracetam is a preferred newer AED for GTCS, add-on therapy for GTCS, and partial seizures. Other newer AEDs are Lacosamide, Topiramate, and Brivaracetam. Older AEDs like sodium valproic acid and phenytoin are still used either alone or as polytherapy esp. with levetiracetam. Both newer and older generation AEDs have their preferred advantages over one another, and individualistic approach is needed in deciding the choice of antiepileptic drug.

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