



## A COMPARATIVE STUDY ON SIDE-EFFECT PROFILE AND EFFECTIVENESS OF LEVETIRACETAM Vs SODIUM VALPROATE IN DIFFERENT TYPES OF EPILEPTIC PATIENTS

Mathew George<sup>\*1</sup>, Lincy Joseph<sup>2</sup>, Anu Lukose<sup>3</sup>, Benita Abraham<sup>4</sup>, Fionna Pulluvattathil<sup>5</sup> and Nimisha Maria Mathew<sup>6</sup>

<sup>1</sup>Professor, Department of Pharmacology, Pushpagiri College of Pharmacy, Thiruvalla, Kerala, India.

<sup>2</sup>Professor, Department of Pharmaceutical Chemistry, Pushpagiri College of Pharmacy, Thiruvalla, Kerala, India.

<sup>3,6</sup>Doctor of Pharmacy (Pharm D) Students, Pushpagiri College of Pharmacy, Thiruvalla, Kerala, India.

**\*Corresponding Author: Dr. Mathew George**

Professor, Department of Pharmacology, Pushpagiri College of Pharmacy, Thiruvalla, Kerala, India.

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### ABSTRACT

**Background:** Since the usage of Levetiracetam is very common nowadays, comparative study of side effect profile and effectiveness of Levetiracetam versus sodium valproate was expected to give more confidence for the use of drugs. The study was aimed to analyse which drug has the lesser side effect profile so as to be prescribed to patients to achieve a positive clinical outcome. **Objectives:** This study attempts to compare side effect profile, effectiveness, quality of life, and medication adherence between Levetiracetam and sodium valproate in different types of epileptic patients. **Patients and Methods:** A prospective observational 6 months study was conducted after IEC approval in 120 newly diagnosed epileptic patients having generalised and partial types of epilepsy taken in two groups. **Results:** It was seen that Levetiracetam was more prescribed to the adult patients while Sodium Valproate was prescribed more to the paediatric patients. From first month to second month NHS3 score, the seizure severity had decreased in case of general type of epilepsy and partial epilepsy, but in case of drug administered, both drug had similar effect in seizure severity. Levetiracetam has less side effects compared to Sodium Valproate in case of general epilepsy. In partial epilepsy, both drugs had similar increase in side effect. The patients showed more adherence to Sodium Valproate when compared with Levetiracetam according to Morisky 8-Item Medication Adherence Scale. Levetiracetam contributed more for the quality of life compared to Sodium Valproate in general, partial and combined type of epilepsy according to QOLIE-31 Scale. **Conclusion:** Levetiracetam is the drug which exhibited lesser adverse effects than sodium valproate, whereas both drugs have equal effectiveness. Levetiracetam group exhibited better quality of life than sodium valproate group. Out of total patients both drug groups have a moderate adherence. It was seen that male population exhibited more development of epilepsy in this study. Thus, according to this study, it can be concluded that both drugs were equally effective in our study population.

**KEYWORDS:** Anti-epileptic drug, Levetiracetam, Sodium Valproate, National Hospital Seizure Severity Scale, Hospital Anxiety And Depression Scale, Quality Of Life In Epilepsy.

### INTRODUCTION

An epileptic seizure is a transient paroxysm of uncontrolled discharges of neurons carrying an event that is discernible by the person experiencing the seizure and/or by an observer. The tendency to have recurrent attacks is known as epilepsy.<sup>[1]</sup> The International Classification of Epileptic Seizure classifies seizures into Partial seizure which begin locally and Generalised seizures which are bilaterally symmetrical without a focal onset.<sup>[2]</sup> For nearly 80% of the patients with epilepsy the underlying etiology is unknown. The most common recognised causes of epilepsy are head trauma and stroke. Developmental and genetic defects are the

cause of about 5% of cases of epilepsy.<sup>[3]</sup> Biochemical changes such as hypoglycaemia, hyperglycemia and hyponatraemia or alcohol abuse also lead to seizures and infections such as meningitis may cause seizures.<sup>[4]</sup> The seizure threshold is a function of the excitability of the neurons as well as the electrical instability of the surrounding tissue.<sup>[5]</sup> Early control of epileptic seizures is important because it allows normalisation of patient lives and prevents acute physical harm and long-term morbidity associated with recurrent seizures. In addition, early control of tonic-clonic seizures is associated with a reduced likelihood of seizure recurrence. Early control of epileptic seizures also correlates with successful

discontinuation of AED treatment after long-term seizure control.<sup>[6]</sup> Most commonly prescribed drugs include Sodium Valproate, Phenytoin, Levetiracetam, Carbamazepine. Sodium Valproate inhibits tonic hind limb extension in maximal electroshock seizures and kindled seizures at non-toxic doses. Levetiracetam exhibits a novel pharmacological profile as it inhibits partial and secondarily generalized tonic-clonic seizures in the kindling model. Mechanism by which Levetiracetam exerts these anti-seizure effects is unknown.<sup>[7]</sup>

The Chalfont Seizure Severity Scale of 1990 was updated and renamed as the National Hospital Seizure Severity Scale. The new version starts with listing as many as three types of seizures. The scale consists of seven questions that are posed for each type of seizure. The Liverpool seizure severity questionnaire was developed with support from Burroughs-Wellcome for use in clinical trials of Lamotrigine. It was designed to evaluate both the severity of ictal events and perceptions of seizures from the perspective of the patient.<sup>[8]</sup> The 8-item Morisky Medication Adherence Scale (MMAS-8) is a structured self-report measure of medication taking behaviour.<sup>[9]</sup> The quality of life in epilepsy inventory (QOLIE-31) contains seven multi-item scales that tap the following health concepts: emotional well-being, social functioning, energy/fatigue, mobility functioning, seizure worry, medication effects, and overall quality of life.<sup>[10]</sup>

## MATERIALS AND METHODS

A prospective observational 6 month study was conducted in the Department of Neuro Medicine, Pushpagiri Medical College Hospital, Thiruvalla. The patients with different types of epilepsy were the study subjects. They were selected on the basis of inclusion and exclusion criteria.

### Inclusion Criteria

- IP / OP patients in Neuromedicine department.
- Newly diagnosed adult and paediatric epileptic patients.
- Both female and male patients.
- Those who give consent voluntarily to participate in the study.
- Patients receiving Levetiracetam and Sodium valproate.

### Exclusion Criteria

- Pregnant women including lactating mothers.
- Patient with psychiatric illness.
- Patients with provoked seizures by comorbidities like CVA, trauma, hyperglycemia, hypoglycemia, tumor, hypotension, fever.
- Patients who are not willing to give consent.

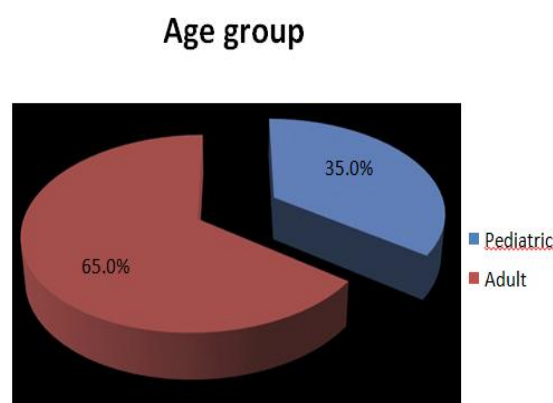
The study was carried out only after obtaining the approval from the IEC. Informed consent was taken from the patient or caregiver. Patients who have been on levetiracetam and sodium valproate were identified and

demographic details of the patients were collected and recorded by using patient data collection form. Patient base line monitoring was done using National Hospital Seizure Severity Scale (NHS3). Questionnaires were used to analyse AED safety (Liverpool Adverse Event Profile), effectiveness (National Hospital Seizure Severity Scale), quality of life (qualy 31), medication adherence (morisky 8 item medication adherence questionnaire).

## RESULTS

**Table No. 1: Distribution Of Patients According To Age.**

Age Group	Frequency	Percent
Pediatric	42	35.0
Adult	78	65.0
Total	120	100.0



**Figure no. 1: Distribtion of patients according to age.**

Out of 120 patients having newly diagnosed epilepsy, 35% of patients belongs to paediatric age category (<18 Years) and remaining 65% of patients belongs to adult age category ( $\geq 18$  Years).

**Table no. 2: Statistical analysis on relationship between age and type of drug administered.**

### Hypothesis

HO: There is no significance relationship between Age group and type of Drug Administered

H1: H0 is false.

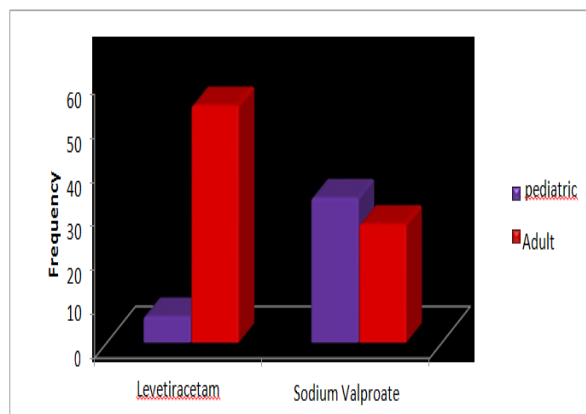
**We reject H0 if p-value less than 0.025.**

Gender	Levetiracetam	Sodium Valproate	Total
Pediatric	6	33	39
Adult	54	27	81
Total	60	60	120

### Chi-square test

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	27.692	1	0.0

**Result:** Here the p-value is  $0.00 < 0.025$ , we reject the null hypothesis. Thus there is a relationship between age group and type of drug administered.

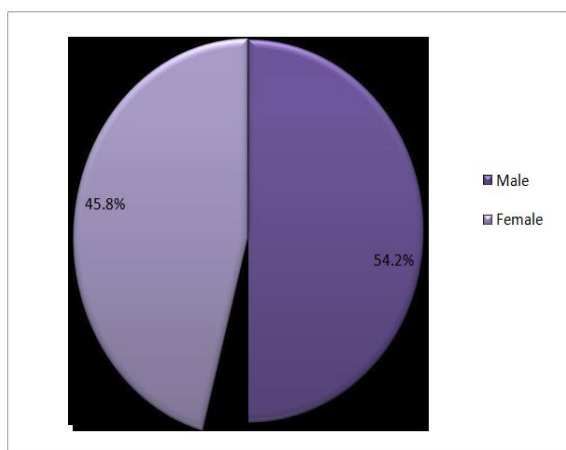


**Figure no.2.**

Out of 60 patients receiving Levetiracetam, 6 belongs to paediatric age and 54 belongs to adult age category. Out of 60 patients receiving Sodium valproate, 33 belongs to paediatric age and 27 belongs to adult age category. This shows that levetiracetam was used mostly among adults and sodium valproate was used among paediatric patients.

**Table no. 3: Distribution of patients according to gender.**

Sex	Frequency	Percent
Male	65	54.2
Female	55	45.8
Total	120	100.0



**Figure no. 3: Distribution of patients according to gender.**

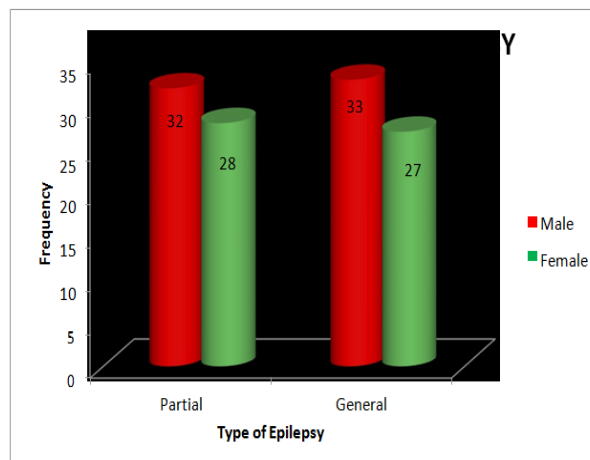
**Table no. 5: Distribution of Patients According To Family History.**

Family History of Epilepsy	Levetiracetam		Sodium Valproate	
	Frequency	Percentage	Frequency	Percentage
Yes	3	5	5	8.3
No	57	95	55	91.7

Out of 120 patients, 45.8% patients are male and 54.2% patients are female.

**Table no. 4: Distribution of gender according to type of epilepsy.**

Gender	Type of epilepsy	
	Partial	General



**Figure no. 4: Distribution of gender according to type of epilepsy.**

Out of 120 patients, In general type of epilepsy, 33 are males and 27 are females and in partial type of epilepsy, 32 are males and 28 are females.

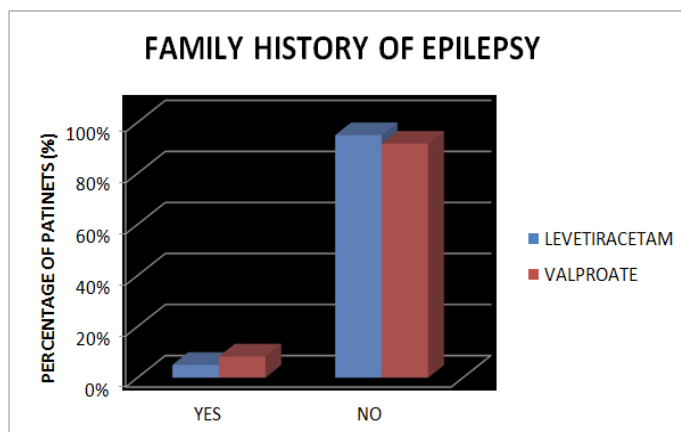


Figure No. 5: Distribution of Patients According To Family History.

Table No. 6: Distribution of Patients Based on Past Medical History.

Past Medical History	LEVETIRACETAM		SODIUM VALPROATE	
	Frequency	Percentage	Frequency	Percentage
Dyslipidemia	6	10	4	6.6
Gout	2	3.3	2	3.3
Osteoarthritis	2	3.3	0	0
Fibromyalgia	8	13.3	6	10

Out of 120 study population with 60 patients on two drug groups, 95% upon Levetiracetam and 91.6% upon Sodium Valproate had no family history. Remaining 5% on Levetiracetam and 8.3% on Sodium Valproate had family history.

as past medical history; Remaining 70.1% had no past medical history. In case of patients who were administered Sodium Valproate, 10% of patients had Fibromyalgia, 6.6% had dyslipidemia, 3.3% had Gout as past medical history; Remaining 80.1% had no past medical history. The above mentioned past medical history do not prompt for onset of epilepsy.

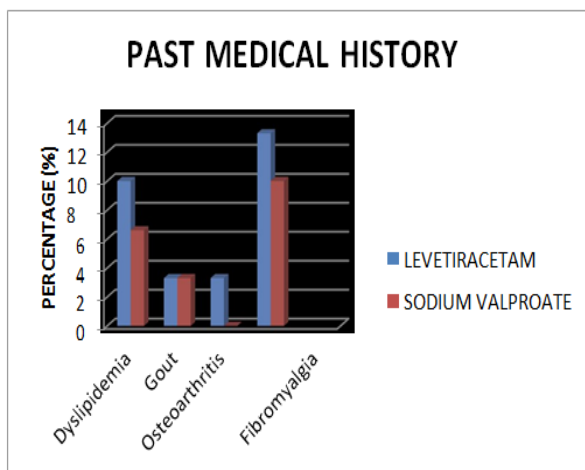
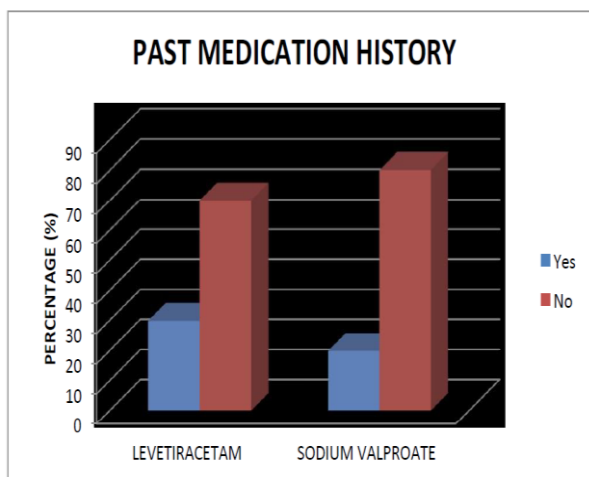


Figure No 6: Distribution of Patients Based on Past Medical History.

Among newly diagnosed epileptic patients, who were administered Levetiracetam, 13.3% had Fibromyalgia, 10% had dyslipidemia, 3.3% had osteoarthritis and Gout

Table No. 7: Distribution of Patients Based on Past Medication History.

Past Medication History	LEVETIRACETAM		SODIUM VALPROATE	
	Frequency	Percentage	Frequency	Percentage
Yes	18	29.9	12	19.9
No	42	70.1	48	80.1



**Figure no. 7: Distribution of Patients Based on Past Medication History.**

Among newly diagnosed epileptic patients, who were administered Sodium Valproate, 80.1% had no past medication history and remaining 19.9% had past medication history. In case of patients who were administered Levetiracetam, 70.1% of patients had no past medication history and remaining 29.9% had past medication history. The above mentioned past medication history do not prompt for onset of epilepsy.

**Table no. 8: Statistical Analysis on Nhs3 Baseline Score and Type of Epilepsy.**

#### HYPOTHESIS

H0: There is no significance difference between NHS3 Baseline Score and type of epilepsy.

H1: H0 is false.

**Table No. 9: Statistical Analysis on Relationship Between Nhs3 First Month and Second Month Score In Types of Epilepsy.**

#### HYPOTHESIS

H0: There is no significant difference between the NHS3 first month and second month score by the use of types drugs administered in type of epilepsy.

H1: H0 is false.

Here we reject the null hypothesis H0 if it's greater than 0.05.

#### MANOVA

Type of epilepsy		Mean square	F	Sig.
General	NHS3 first and second month score	644.033	172.191	.000
	NHS3 first and second month score with drug	.033	.009	.925
Partial	NHS3 first and second month score	567.675	309.398	.000
	NHS3 first and second month score with drug	.408	.223	.639

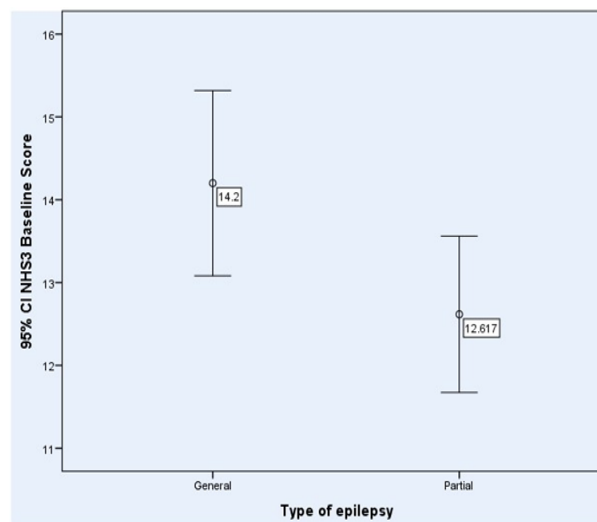
**Result:** Here in general type of epilepsy NHS3 First Month and Second Month Score after use of drugs, p-value 0.000 is less than 0.05. It indicated that there was a decrease in seizure severity after use of drugs. In case of NHS3 First Month and Second Month Score compared with drug administered, the p-value 0.925 is greater than 0.05 means that there is similar effect in using Levetiracetam and Sodium Valproate.

We reject H0 if p-value less than 0.025.

	Type of epilepsy	Mean	Std. Deviation
NHS3 Baseline Score	General	14.2	4.329
	Partial	12.62	3.65

T	Df	Sig. (2-tailed)
2.166	118	0.32

**Result:** Here p-value obtained is 0.32 is greater than 0.025. It indicated that seizure severity was similar in both type of epilepsy.



**Figure No 8: Statistical Analysis on Nhs3 Baseline Score and Type of Epilepsy.**

Here in partial type of epilepsy NHS3 First Month and Second Month Score after use of drugs, p-value is 0.000 is less than 0.05. It indicated that there was decrease in seizure severity after use of drugs. In case of NHS3 First Month and NHS3 Second Month Score compared with drug administered, the p-value is 0.639 greater than 0.05 means that there is similar effect in using Levetiracetam and Sodium Valproate.

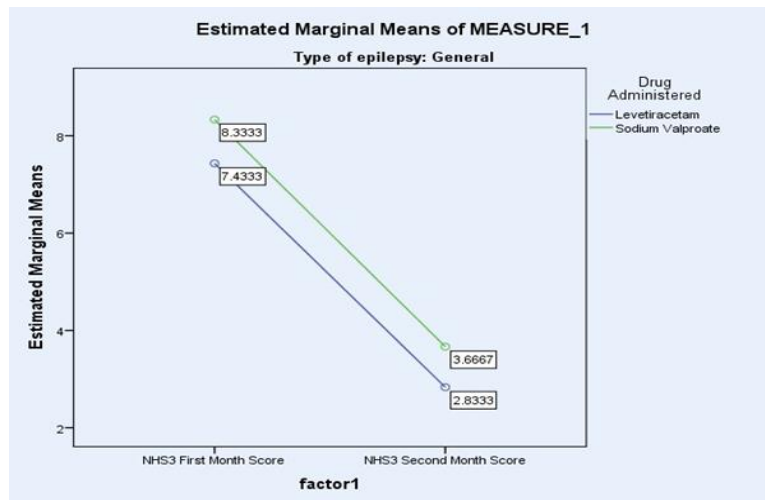


Figure No. 9.1: Relation Between Nhs3 First-Second Month Score with Drugs in General Epilepsy.

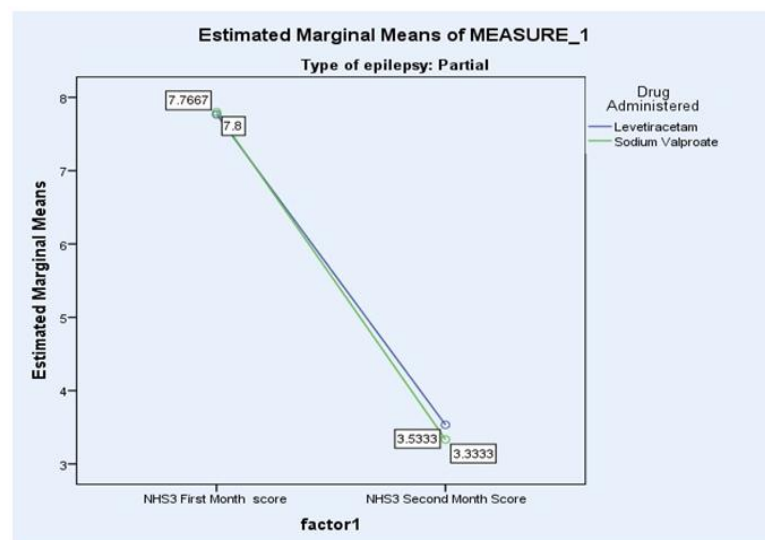


Figure No. 9.2: Relation Between Nhs3 First-Second Month Score With Drugs In Partial Epilepsy.

From the above graphs, in both types of epilepsy NHS3 score had decreased, showing that both drugs were equally effective.

Table no. 10 Statistical Analysis on Relationship Between liverpool Adverse Events Profile-First And Secondmonth in Types of Epilepsy.

**HYPOTHESIS**

H0: There is no significant difference between the Liver Pool Adverse Events Profile – First Month and Liver Pool Adverse Events Profile - Second Month by the use of types drugs administered in type of epilepsy.

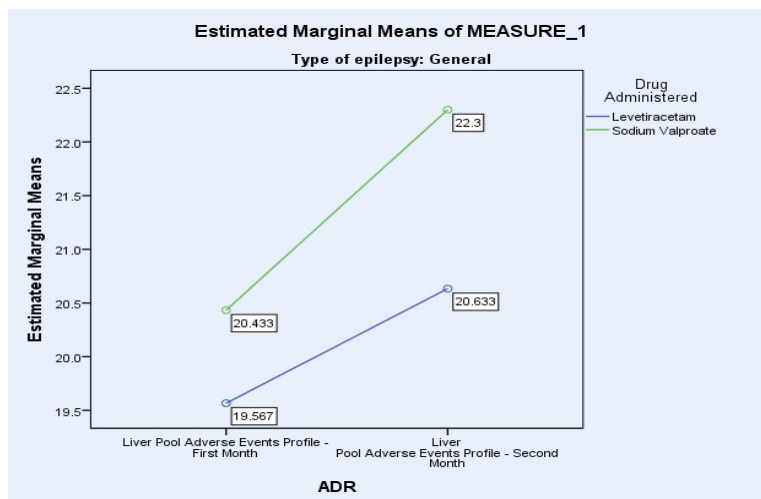
H1: H0 is false.

Here we reject the null hypothesis H0 if it's greater than 0.05.

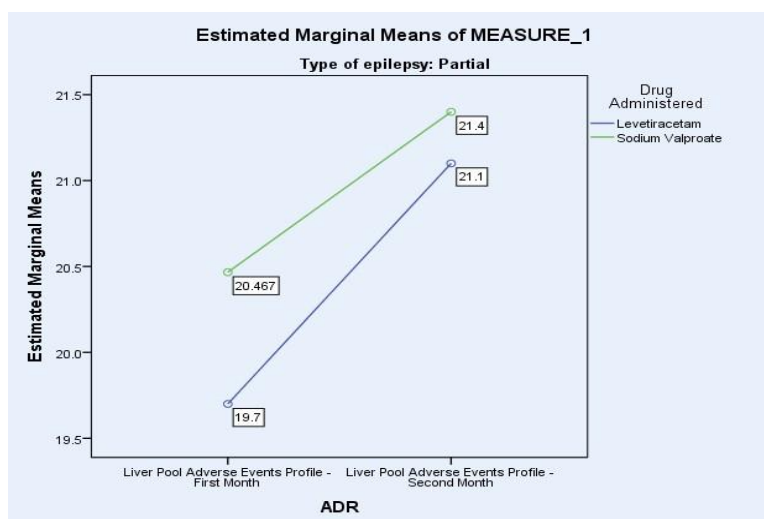
Types of epilepsy		Mean square	F	Sig.
General	Liver Pool Adverse Events Profile - First Month And Second Month score	64.533	55.314	.000
	Liver Pool Adverse Events Profile - First Month and Second Month score with Drugs	4.800	4.114	.047
Partial	Liver Pool Adverse Events Profile - First Month and Second Month score	40.833	30.645	.000
	Liver Pool Adverse Events Profile - First Month and Second Month score with Drugs	1.633	1.238	.270

**Result:** Here in general type of epilepsy, Liver Pool Adverse Events Profile – First Month and Second Month score after use of drugs, p-value is 0.000 is less than 0.05, that indicates there is an increase in LAEP score. In case of Liver Pool Adverse Events Profile - First Month and Second Month score compared with drug administered, the p-value is 0.047 less than 0.05 means that Levetiracetam has less side effect compared to Sodium valproate.

Here in partial type of epilepsy, Liver Pool Adverse Events Profile - First Month and Second Month score after use of drugs, p-value is 0.000 is less than 0.05, that indicates there is an increase in LAEP score. In case of Liver Pool Adverse Events Profile - First Month and second Month score compared with Drug administered, the p-value is 0.270 greater than 0.05 means that both drugs showed similar increase in side effect.



**Figure No. 10.1: Relationship Between Liverpool Adverse Events Profile-First And Second Month In General Epilepsy.**



**Figure no. 10.2: Relationship Between Liverpool Adverse Events Profile-First And Second Month In Partial Epilepsy.**

From the above graphs, in both types of epilepsy LAEP score had increased. In general epilepsy Levetiracetam had less side effect whereas in partial epilepsy both drug had similar increase in side effects.

#### COMPARISON OF EACH DRUG IN DIFFERENT TYPE OF EPILEPSY IN LAEP HYPOTHESIS

H<sub>0</sub>: There is no significant difference between the type of epilepsy in Liver Pool Adverse

Events Profile - First Month and Liver Pool Adverse Events Profile - Second Month by the use of types drugs administered.

H<sub>1</sub>: H<sub>0</sub> is false.

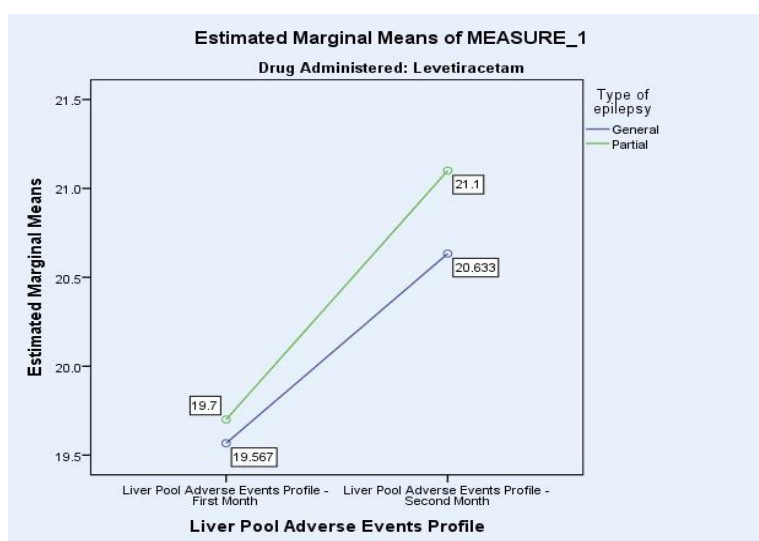
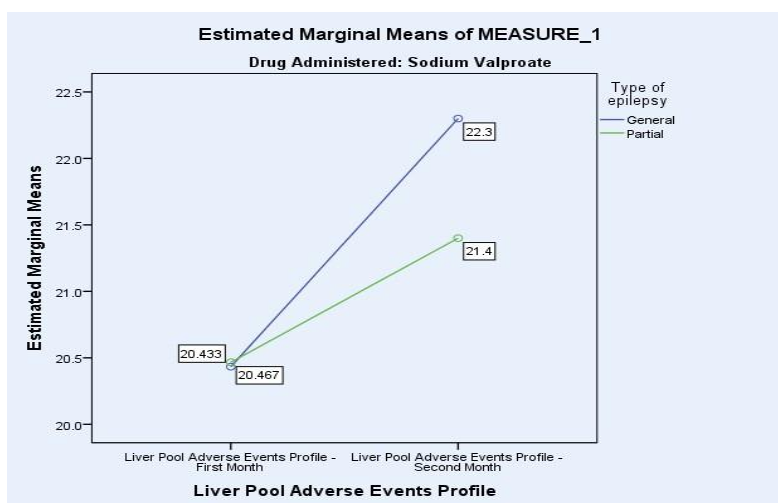
Here we reject the null hypothesis H<sub>0</sub> if it's greater than 0.05.

**Table No.11: Comparison of Liverpool Adverse Event Profile Firstmonth: Second Month Score And Drug Administered.**

Types of Drugs		Mean square	F	Sig.
Levetiracetam	Liver Pool Adverse Events Profile - First Month and Second Month score	45.633	41.65	.000
	Liver Pool Adverse Events Profile - First Month and Second Month score with type of epilepsy	0.833	0.761	.387
Sodium valproate	Liver Pool Adverse Events Profile - First Month and Second Month score	58.800	42.27	.00
	Liver Pool Adverse Events Profile - First Month and Second Month score with type of epilepsy	6.533	4.698	.034

**Result:** Levetiracetam showed an increase in Liver Pool Adverse Events Profile – First Month and Second Month score, since p value is less than 0.05. In case of Liver Pool Adverse Events Profile - First Month and Second Month score compared with type of epilepsy, p value is 0.387 greater than 0.05, which showed similar increase in side effect by Levetiracetam in both type of epilepsy.

Sodium Valproate showed an increase in Liver Pool Adverse Events Profile - First Month and Second Month score, since p value less than 0.05. In case of Liver Pool Adverse Events Profile - First Month and Second Month score compared with type of epilepsy p value is 0.034 less than 0.05, showed increased side effect in general epilepsy.

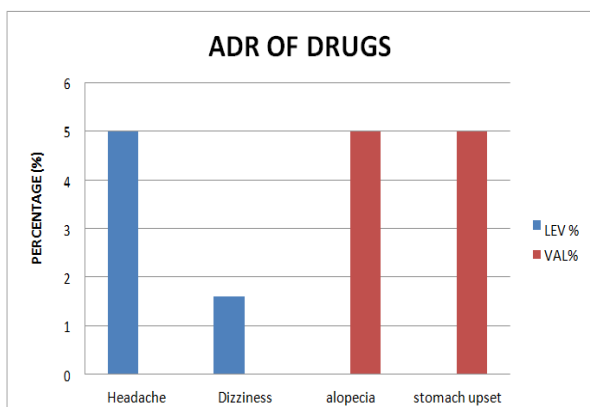
**Figure No. 11.1: Comparison of Liverpool Adverse Event Profile First Month: Second Month Score-Type of Epilepsy and Levetiracetam.****Figure no. 11.2: Comparison of Liverpool Adverse Event Profile First Month: Second Month Score-Type of Epilepsy and Sodium Valproate.**



From the above graphs both drugs showed increase in LAEP scores, Sodium valproate showed greater increase in side effect in general epilepsy, whereas Levetiracetam had similar side effect in both type of epilepsy.

**Table no. 12: ADR reported on laep.**

ADR	Levetiracetam	Lev %	Sodium valproate	Val %
Headache	3	5	0	0
Dizziness	1	1.6	0	0
alopecia	0	0	3	5
stomach upset	0	0	3	5



**Figure No. 12: ADR Reported on Laep.**

Among 120 patients, 60 on each drug group:

- Levetiracetam showed 5% Headache and 1.6% Dizziness.
- Sodium valproate showed 5% Alopecia and 5% Stomach upset.
- It was based upon the observations made in the Liverpool Adverse Event Profile.

**Table No. 13: Statistical Analysis on Relationship Between Medication Adherence and Type of Drug Administered.**

**HYPOTHESIS**

HO: There is no significance relationship between Medication Adherence and type of Drug Administered

H1: HO is false.

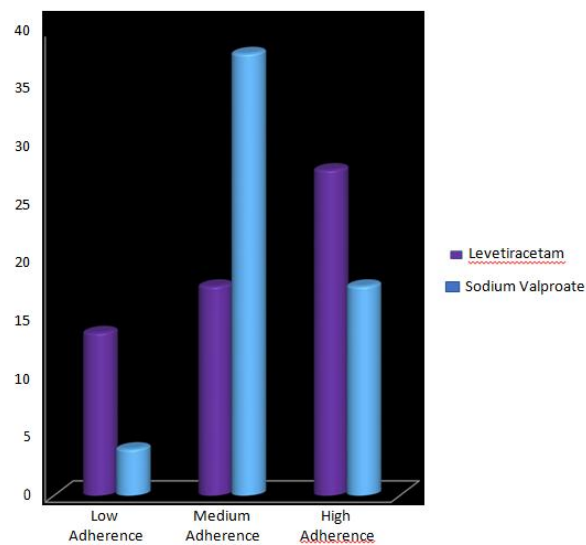
**We reject H0 if p-value less than 0.025**

Medication Adherence	Levetiracetam	Sodium Valproate
Low Adherence	14	4
Medium Adherence	18	38
High Adherence	28	18
Total	60	60

**Chi-square tests**

	Value	df	Asymp. (2-sided)	Sig.
Pearson Chi-Square	17.434	2	0.001	

**Result:** The p-value obtained is 0.001 less than 0.025. Thus we reject the null hypothesis. From this we can understand that most of the patient showed more adherence to sodium valproate when compared with Levetiracetam.



**Figure no. 13: Relationship Between Medication Adherence and Type of Drug Administered.**

**Result:** From the graph, it is evident that most of the patients showed, more adherence to Sodium Valproate compared with Levetiracetam.

**Table no. 14: comparison of Qolie-31: Type of Epilepsy and Drug Administered.****HYPOTHESIS**

HO: There is no significance relationship between Quality of Life and type of Drug Administered in type of epilepsy general and partial.

H1: HO is false.

**We reject H0 if p-value less than 0.025**

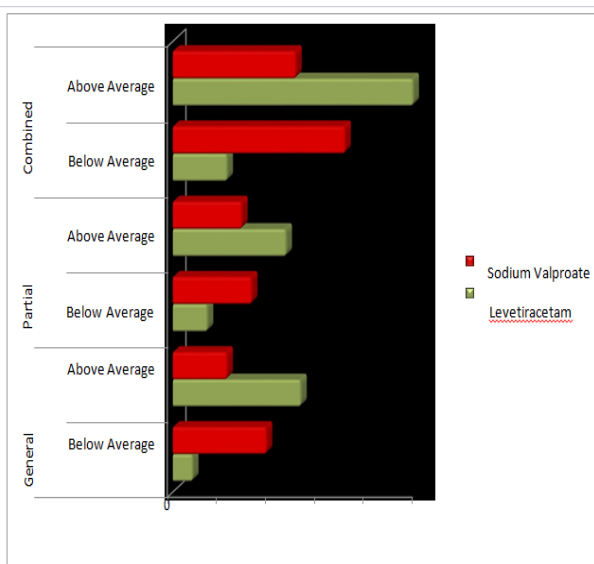
Type of epilepsy	Quality of Life	Drug Administered		Total
		Levetiracetam	Sodium Valproate	
General	Below Average	4	19	23
	Above Average	26	11	37
	Total	30	30	60
Partial	Below Average	7	16	23
	Above Average	23	14	37
	Total	30	30	60
Total	Below Average	11	35	46
	Above Average	49	25	74
	Total	60	60	120

**CHI SQUARE TEST**

Type of epilepsy	Pearson Chi-Square Value	df	Asymp. Sig. (2-sided)
General	15.864	1	.000
Partial	5.711	1	.017
Total	20.306	1	.000

**Result:** The general, partial and total (general and partial) type of epilepsy has the p values 0.000, 0.017 and 0.000 respectively. In all the type of epilepsy, the p value is less than 0.025. Thus we reject the null hypothesis. It is understood that in combined, general and partial type of epilepsy, the drug Levetiracetam contributed more for the quality of life compared to drug Sodium Valproate.

**Result:** From the graph we can that the frequency of occurring above average quality of data is high in both type of epilepsy and also in combined type of epilepsy. So we can conclude that in combined, general and partial type of epilepsy, the drug Levetiracetam contributed more for the quality of life compared to drug Sodium Valproate.

**CONCLUSION**

An Epilepsy is a chronic disorder which is characterized by recurrent epileptic seizures that occur unexpectedly and stops spontaneously. In this study we attempt to compare the Side effect profile and Effectiveness of Levetiracetam Vs Sodium Valproate in different types of epileptic patients. The current study was conducted in Neuromedicine department of Pushpagiri Medical College Hospital, Thiruvalla. 120 newly diagnosed epileptic patients having generalised and partial types of epilepsy were selected for the study and they were divided into two groups, one taking Levetiracetam (n=60) and the other group taking Sodium Valproate (n=60). Their seizure severity was monitored on the starting day of the therapy and after first and second months follow up. The obtained parameters were analysed and the results concluded that Levetiracetam is the drug which exhibited lesser adverse effects than Sodium Valproate, whereas both drugs have equal effectiveness. Levetiracetam group

exhibited better quality of life than Sodium Valproate group. Among the patients, Sodium Valproate showed more adherence than Levetiracetam. Thus, according to this study, it can be concluded that both drugs were equally effective in our study population. For severe recurrent seizures, Sodium valproate can be given as first line agent, especially in pediatric patients. It has been seen that Levetiracetam has a greater prescribing trend in adult patients due to its higher quality of life.

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