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# A cross-sectional comparative study to evaluate the efficacy and safety of levetiracetam with other antiepileptics among epileptic patients at a tertiary care teaching hospital

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## Abstract

**Background:** Epilepsy is a neurological disorder characterized by recurrent seizures, and about one-third of patients do not respond to a single antiepileptic drug (AED). Levetiracetam (LEV) is commonly used as a first-line treatment for partial seizures and in combination with other AEDs. This study aimed to determine which combination therapy with LEV is more effective and safer for treating focal epilepsy.

**Method:** The study analyzed 90 patients diagnosed with focal epilepsy, who were treated with LEV in combination with other AEDs. The efficacy was assessed by comparing the seizure count before and after combination therapy, and safety was evaluated based on adverse effects. Statistical analysis was performed using IBM SPSS 22.0.

**Result:** There were five groups in which levetiracetam was used in combination with other AED

- Group A: Levetiracetam + Lacosamide
- Group B: Levetiracetam + Clobazam
- Group C: Levetiracetam + Oxcarbazepine
- Group D: Levetiracetam + Sodium valproate
- Group E: Levetiracetam + Phenytoin

Due to an insufficient sample size, only Group A (LEV-LCM) and Group B (LEV-CLB) were statistically analyzed. The t-values for these groups were 15.132 and 13.889, respectively, both statistically significant with a p-value <0.001.

**Conclusion:** The results from this study showed that the addition of a second AED significantly reduced the seizure count when compared with a single AED regimen. LEV-LCM & LEV-CLB combination were taken for the analysis of safety and efficacy. It was found that there was a significant difference in seizure count within the groups with a p value <0.001. Comparing the t test value, it was found that the addition of LCM to LEV produce a greater difference in seizure count. Only a few minor side effects were observed in both the groups

**Keywords:** Antiepileptic drug; Levetiracetam; Lacosamide; Clobazam

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## 1. Introduction

A seizure is a paroxysmal event characterized by abnormal, excessive, hypersynchronous discharge of cortical neuron activity. Epilepsy is defined by the occurrence of at least two unprovoked seizures with or without convulsions separated by at least 24 hours.[1]

The ultimate goal of treatment for epilepsy is to achieve complete seizure freedom with minimal to no side effects, thus enabling patients to maintain an optimal quality of life.[2] AEDs work by raising the threshold of neurons to electrical or chemical stimuli, stabilizing neuronal membranes or by limiting the propagation of seizure discharges, reducing synaptic transmission and nerve conduction.[3]

Initial treatment typically involves monotherapy to minimize adverse effects and simplify the regimen. If monotherapy is ineffective, combination therapy with AEDs that have different mechanisms of action may be considered.[4] Drugs for monotherapy include levetiracetam, lamotrigine, sodium valproate, phenytoin etc. Monitor the patient's response to treatment, side effects, and seizure control. Monotherapy with older AEDs may not provide seizure freedom for many patients and may cause significant side effects.[5] Newer AEDs may offer improved efficacy with fewer side effects and are often considered when balancing seizure frequency and drug side effects.

Despite appropriate AED treatment, approximately 30% to 35% of patients will be refractory to treatment. The percentage of patients who are seizure free on one drug varies by seizure type. Drugs can be combined in an attempt to help the patients become seizure free. Combining AEDs with different mechanism of action can be advantages. [6]

An ideal add on AED should be safer, have a better pharmacodynamic and pharmacokinetic profile to minimize interaction and adverse events.[7] LEV is a new antiepileptic drug, structurally and mechanistically dissimilar to other marketed AEDs. It is effective in reducing seizures in patients with epilepsy both as adjunctive treatment and as monotherapy. LEV has many therapeutic advantages for patients with epilepsy. It has favorable pharmacokinetic characteristic (good bioavailability, linear pharmacokinetics, insignificant protein binding, lack of hepatic metabolism, rapid achievement of steady state concentration and a low potential for drug-drug interaction).[8] Thus, now a days LEV is used as a first line agent in treating epilepsy. This study aimed to find out the safety and efficacy of combination therapy in epilepsy with LEV.

## 2. Material and methods

This was a cross-sectional comparative study conducted at a tertiary care hospital on 90 epilepsy patients for a period of 6 months.

Both inpatients and outpatients diagnosed with focal epilepsy with or without secondary generalization, patients receiving combination of AEDs with LEV, patients of age 18 years, patients of all gender were included in the study. Pregnant and lactating women, patients with comorbidities leading to seizure were excluded.

The efficacy was analyzed by comparing the seizure count before and after combination and safety was analyzed by comparing the adverse effects. The data were entered into Microsoft Excel Spreadsheet and Statistical analysis was performed by IBM SPSS 22.0.

After obtaining permission from the IEC, study began with data collection. Case records were retrospectively and prospectively reviewed for demographic data, clinical presentations, investigations, management and adverse reactions.

## 3. Results and discussion

A total of 90 patients met with the inclusion criteria were included in the study

**Table 1** Frequency and percentage distribution of samples according to gender N=90

| Sex | Frequency | Percentage (%) |
|---|---|---|
| MALE | 42 | 47 |
| FEMALE | 48 | 53 |

**Inference:** This data shows that out of the 90 samples of epilepsy patients about 48 were females and 42 were males.

**Table 2** Frequency and percentage distribution of samples according to age in years N=90

| Age in years | Frequency | Percentage (%) |
|---|---|---|
| 18 – 38 YEARS | 28 | 31.2 |
| 39 - 58 YEARS | 24 | 26.7 |
| 59 – 78 YEARS | 32 | 35.5 |
| 79 – 98 YEARS | 6 | 6.6 |

About 35.5% of patients where in age group of 59-78 years. Then maximum percentage of patients (31.2 %) where in age group of 18-38 years. About 26.7 % of patients where in age group of 39-58 years. The least percentage of patients about 6.6% where in age group of 79-98 years

**Table 3** Frequency and distribution of samples according to medication combination N=90

| Medication combination | Frequency | Percentage (%) |
|---|---|---|
| LEV + LCM | 40 | 44 |
| LEV + CLB | 40 | 44 |
| LEV + OXC | 4 | 5 |
| LEV + SODIUM VALPROATE | 4 | 5 |
| LEV +PHT | 2 | 2 |

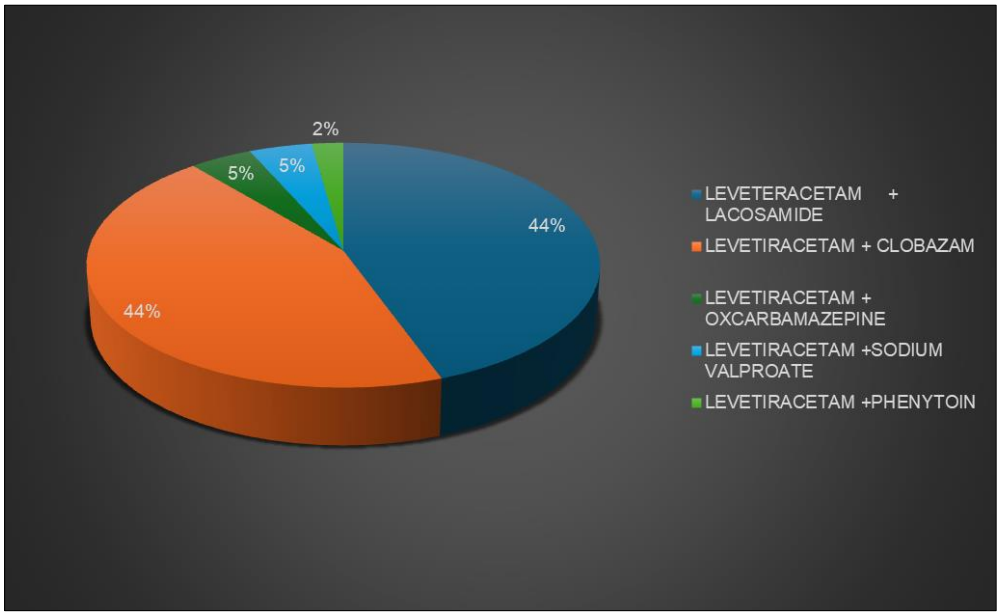


**Figure 1** Percentage distribution of samples according to medication

**Inference:** The above data shows various combination of AED with LEV was tried to find out and among the numerous combination LEV-LCM and LEV-CLB was prescribed the most. Other combinations are LEV-PHT, LEV-OXC and LEV-Sodium valproate.

**Table 4** Comparison of mean seizure count between various groups before and after addition of add on AEDN=90

| MEDICATIONS | BEFORE COMBINATION (MEAN± SD) | AFTER COMBINATION (MEAN±SD) |
|---|---|---|
| LEV+ LCM (GROUP A) | 1.31±0.43 | 0.66±0.34 |
| LEV+ CLB (GROUP B) | 1.10±0.34 | 0.58±0.28 |
| LEV+ OXC (GROUP C) | 1.35±0.25 | 0.60±0.23 |
| LEV+ SODIUM VALPROATE (GROUP D) | 1.20±0.16 | 0.65±0.25 |
| LEV+PHT (GROUP E) | 1.10±0.14 | 0.40±0.28 |

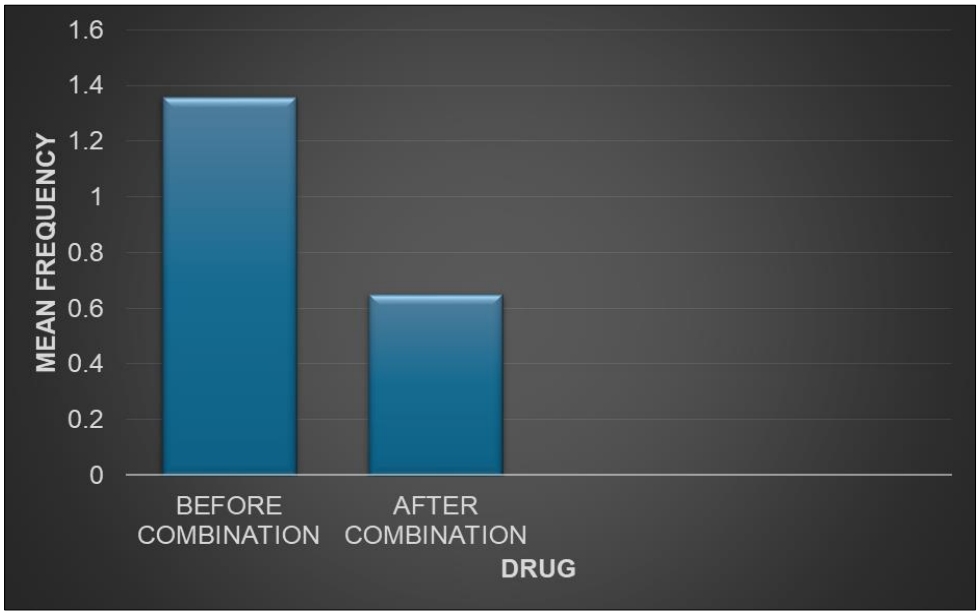


**Figure 2** Mean seizure count before and after combination in group A(LEV+ LCM)

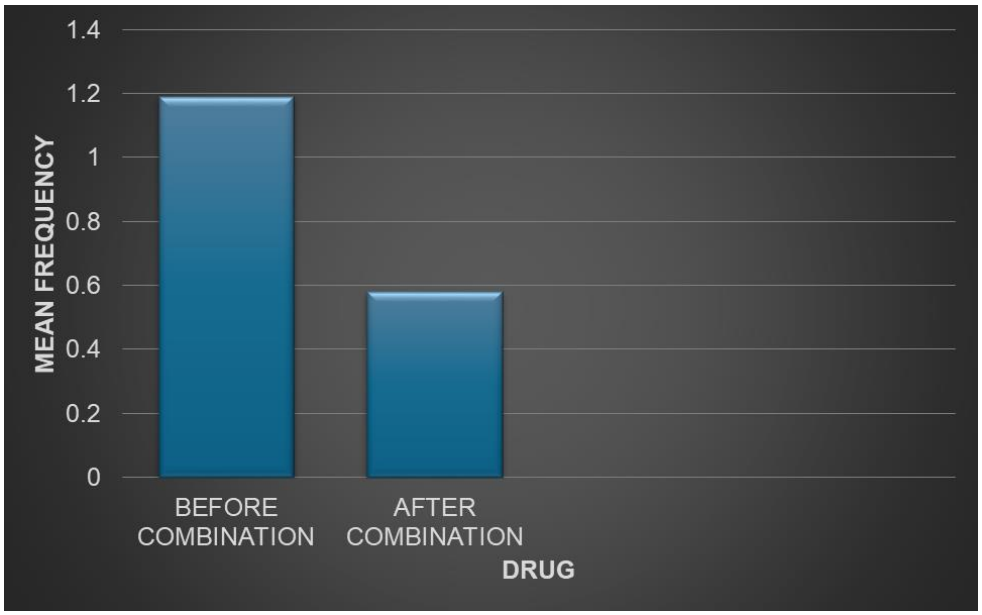


**Figure 3** Mean seizure count before and after combination in group B (LEV+ CLB)

**Inference:** The mean seizure frequency(±SD) in various groups before and after the addition of the second antiepileptic agent is as follows.

- In group A the mean seizure frequency(±SD) before the addition of LCM was 1.31(±0.43) and after the addition of LCM it gets reduced to 0.66(±0.34).
- In group B the mean seizure frequency(±SD) before the addition of CLB was 1.10(±0.34) and it get reduced to 0.58(±0.28) after the addition of CLB.
- In group C the mean seizure frequency(±SD) before the addition of OXC was 1.35(±0.25) and it get reduced to 0.60(±0.23) after the addition OXC.
- In group D the mean seizure frequency(±SD) before the addition of sodium valproate was 1.20(±0.16) and it get reduced to 0.65(±0.25) after the addition of sodium valproate.
- In group E the mean seizure frequency(±SD) before the addition of PHT was 1.10(±0.14) and it get reduced to 0.40(±0.28) after the addition PHT.

**Table 5** Mean, standard deviation, mean difference, t value and p value of seizure count before and after drug combination within the groups

| Drug | Time | Min | Max | Mean | Standard deviation | Mean difference | t value (paired t test) | p value |
|---|---|---|---|---|---|---|---|---|
| LEV+LCM (GROUP A) (N=40) | Before combination | 0.60 | 2.20 | 1.31 | 0.43 | 0.65 | 15.132 | <0.001*** |
| | After combination | 0.60 | 2.00 | 0.66 | 0.34 | | | |
| LEV+CLB (GROUP A) (N=40) | Before combination | 0.20 | 1.40 | 1.10 | 0.34 | 0.53 | 13.889 | <0.001*** |
| | After combination | 0 | 1.40 | 0.58 | 0.28 | | | |

***Significant at 0.001 level n = 80

**Inference:** The above data shows the mean seizure frequency(±SD) before addition of LCM in group A was 1.31(±0.43) which get reduced to 0.66(±0.34) after addition of LCM. The t test value was found to be 15.132 with a p value <0.001 and was found to be statistically significant.

The mean seizure frequency (±SD) before addition of CLB in group B was found to be 1.10(±0.34) which get reduced to 0.58(±0.28) after the addition CLB. The t test value was found to be 13.889 with a p value <0.001 and was found to be statistically significant.

Since the mean difference and t test value in group A where LCM was added as the second line agent was found to be higher, it can be concluded that the addition of LCM to LEV produce more difference in seizure frequency, so LCM is a better adjunctive compared to CLB.

**Table 6** Mean standard deviation, mean difference, t value and p value of seizure count between the groups

| Group | Min | Max | Mean | Standard deviation | Mean difference | t value (unpaired t test) | p value |
|---|---|---|---|---|---|---|---|
| Group A (LEV+LCM) (N=40) | 0.60 | 2.00 | 0.66 | 0.34 | 0.09 | 1.215 | 0.228 (NS) |
| Group B (LEV+CLB) (N=40) | 0 | 1.40 | 0.58 | 0.28 | | | |

***Significant at 0.001 level, NS- Not Significant n= 80

**Inference:** The mean seizure frequency after addition of LCM in group A was 0.66(±0.34) and it was 0.58(±0.28) in group B where CLB was added. The t test value was 1.215 with a p value of 0.228, which was statistically nonsignificant.

**Table 7** Frequency and distribution of samples according to adverse effects N=90

| DRUGS | Sedation | Forgetfulness | Headache | Dizziness | Fatigue | Imbalance |
|---|---|---|---|---|---|---|
| LEV+ LCM | 20 | 16 | 17 | 8 | 18 | 4 |
| LEV+ CLB | 20 | 23 | 19 | 4 | 17 | 5 |
| LEV+ PHT | 1 | 0 | 1 | 1 | 0 | 0 |
| LEV+ OXC | 3 | 3 | 1 | 4 | 0 | 0 |
| LEV+ Sodium Valproate | 3 | 3 | 1 | 4 | 0 | 0 |
| Total | 47 | 45 | 40 | 15 | 41 | 10 |

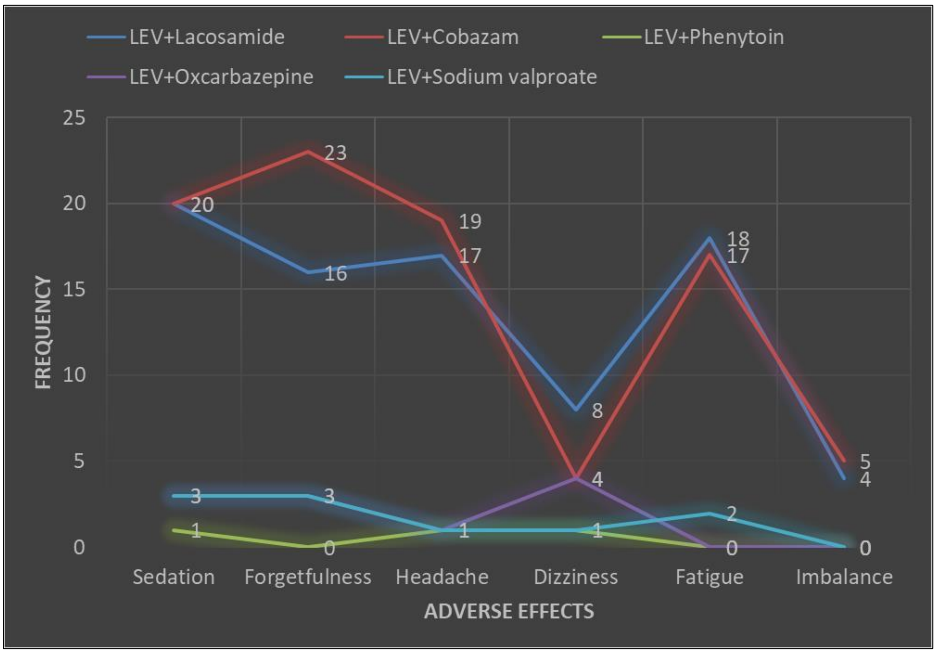


**Figure 4** Adverse Effects

**Inference:** The above table shows the frequency and percentage distribution of samples according to adverse effects. Sedation, forgetfulness, headache, dizziness, fatigue and imbalance were the most

frequently encountered ADRs. In LEV-LCM group about 20 patients reported sedation, 16 reported forgetfulness, 17 reported headache, 8 reported dizziness, 18 reported fatigue and 4 reported imbalance.

In the LEV-CLB group about 20 patients had sedation, 23 patients had forgetfulness, 19 patients had headache, 4 patients had dizziness, 17 had fatigue and 5 patients had imbalance.

In the LEV-PHT group 1 patient reported sedation, 1 patient reported headache and 1 patient reported dizziness.

In the LEV-OXC group, 3 patients reported sedation, 3 patient reported forgetfulness, 1 patient reported headache and 4 patient reported dizziness.

In the LEV-sodium valproate group 3 patients reported sedation,3 patients reported forgetfulness, 1 patient reported headache and 4 patient dizziness.

**Table 8** Association of ADR between patients received LCM and CLB as adjuvant N=80

| Sl. No | Demographic variables | Drug | | Total | $\chi^2$ test |
|---|---|---|---|---|---|
| | | LCM (N=40) | CLB (N=40 | | |
| 1 | Sedation | 20 | 20 | 40 | $\chi^2$=0.001, df=1, p=0.999 (NS) |
| 2 | Forget fullness | 16 | 23 | 39 | $\chi^2$=2.452, df=1, p=0.117 (NS) |
| 3 | Headache | 17 | 19 | 36 | $\chi^2$=0.202, df=1, p=0.653 (NS) |
| 4 | Dizziness | 8 | 4 | 12 | $\chi^2$=1.569, df=1, p=0.210 (NS) |
| 5 | Fatigue | 18 | 17 | 35 | $\chi^2$=0.051, df=1, p=0.822 (NS) |
| 6 | Imbalance | 4 | 5 | 9 | $\chi^2$=0.125, df=1, p=0.723 (NS) |

**Inference:** The above data shows that in group A and B 20 patients reported sedation as side effect and the data was statistically nonsignificant value=0.999

In group A about 16 patients and in group B about 23 patients reported forgetfulness as side effect and the data was statistically nonsignificant, p value=0.117

17 patients in group A and 19 patients in group B reported headache as side effect and the data was statistically nonsignificant, p value=0.653

8 patients in group A and 4 patients group B reported dizziness as side effect and it was statistically nonsignificant, p value=0.21018 patients in group A and 17 patients in group B reported fatigue and it was statistically non-significant, p value=0.822 4 patients in group A and 5 patients in group B reported imbalance, and it was statistically non-significant value=0.723

## 4. Conclusion

Approximately one third of the epilepsy cases cannot be controlled with a single AED. Therefore, the use of combinations of AEDs is recommended for better safety and efficacy. Levetiracetam (LEV) is structurally and mechanistically different from other AEDs. It is a newer drug used as an adjuvant with other AED since the year 2000 which was later used in partial seizures as first line agent.

In this study, safety and efficacy of combination therapy of LEV with other AEDs were assessed. It is observed from the study that the most prescribed combinations of AEDs were Levetiracetam-Lacosamide and Levetiracetam-Clobazam. Therefore, these two combinations were analyzed.

The efficacy of two drug combinations were compared using seizure count. There was a significant difference in seizure count within the groups, with a p-value < 0.001. The comparison of t-test values indicated that, the addition of lacosamide to levetiracetam produced a greater difference in seizure count. Minor ADRs were observed in both groups. However, there was no significant difference between them. The most encountered adverse drug reactions (ADRs) include sedation, forgetfulness, dizziness, headache, imbalance and fatigue.

## Compliance with ethical standards

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*Disclosure of conflict of interest*

None Declared

*Statement of ethical approval*

The study was approved by the Institutional Ethics Committee.

*Statement of informed consent*

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

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