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A PROSPECTIVE COMPARATIVE STUDY OF EFFICACY AND SAFETY OF LEVETIRACETAM AND CARBAMAZEPINE AS MONOTHERAPY IN FOCAL SEIZURES

Aramalla Naga Priyanka[1], Nagarjuna B[2], Nagaraju Reddycherla[3], K Kiran Kumar[4]

[1]Assistant Professor, Department of Pharmacology, Mediciti Institute of Medical Sciences, Hyderabad, India
[2]Assistant Professor, Department of Neurosurgery, Osmania Medical college, Hyderabad, India
[3]Associate Professor, Department of Neurosurgery, Government Medical College, Wanaparthy, India
[4]Assistant Professor, Department of Neurosurgery, Government Medical College, Nizamabad, India

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Corresponding Author:

Dr. Nagaraju Reddycherla
Associate Professor, Department of Neurosurgery, Government Medical College, Wanaparthy, India

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ABSTRACT

Background: Focal epilepsies are common, for instance, 53% of cases of epilepsy in children were focal-onset in an Indian study. Carbamazepine (CBZ) has long been a first line agent for new onset "focal" seizures, however it has a number of side effects (sedation, rash, hyponatremia, blood dyscrasias). Levetiracetam (LEV) is a newer antiepileptic drug that acts via a novel mechanism (SV2A binding), has a favorable pharmacokinetics, and has limited drug interactions and is well tolerated. LEV or lamotrigine are now recommended as first-line treatment for focal seizures in adults and children. The aim of our study was to compare the efficacy and safety of LEV against CBZ monotherapy in patients with focal seizures. **Methods:** This is a prospective, open-label, comparative study in which 60 patients who were newly diagnosed with focal epilepsy were randomly assigned 1:1 to LEV or CBZ monotherapy. Baseline demographics (age, sex, number of seizures, EEG/ MRI results) were taken (Table 1). Patients were given LEV (500 mg daily, and increased to 1000–1500 mg daily) or CBZ (200 mg twice daily, increased to 400–800 mg daily). Seizure frequency and adverse events were clinically evaluated monthly for 6 months. Laboratory monitoring (CBC, LFTs) was carried out at baseline and quarterly. The primary endpoint was whether seizures were free at 6 months. Secondary endpoints were seizure reduction, retention rate and side effect profile. Data were analyzed statistically with t-test and Chi-square test (SPSS version 25) and significant level was set at $p<0.05$. **Results:** At baseline the two groups (n = 30 in each) were not different in terms of mean age (~28–30 years) or sex or pre-treatment seizure frequency (Table 1). At 6 months, 60% of the CBZ group and 73% of the LEV group were seizure free ($p\approx0.2$, not statistically significant). Overall responder rates (≥50% reduction in seizures) were similar (83% CBZ vs 90% LEV). In both groups, seizure frequency significantly decreased in the mean during the month (Table 2). The most frequent CNS side effects of CBZ therapy were drowsiness (in ~20% of patients) and LEV therapy, neuropsychiatric complaints (in ~17% of patients) (Table 3). No serious rash or organ toxicity was observed in either arm.There were few severe adverse events in either arm. 2 patients in the LEV group were withdrawn early due to intolerable agitation and 1 CBZ patient due to dizziness. The study flow is shown in Figure 1, baseline characteristics, outcomes, and adverse events in Tables 1-3. **Conclusions:** In this cohort, there was no difference in seizure control between LEV and CBZ monotherapy in focal epilepsy. As previously reported, LEV had a numerical advantage in seizure freedom, but this difference was not statistically significant. The good safety profile and simplicity of use (no routine blood monitoring) of LEV may be good options. LEV is the preferred option in many settings, but CBZ is an effective alternative based upon recent evidence and guideline recommendations. The results from this study support the monotherapy use of LEV for focal seizures, and that either drug can be effective when used appropriately.

Keywords: *Focal epilepsy, levetiracetam, carbamazepine, monotherapy, efficacy, safety.*

INTRODUCTION

Epilepsy is a frequent neurological disorder and focal (partial) seizures represent a major type of epilepsy. Focal-onset seizures are more common in India; a recent epidemiological survey of children with epilepsy in rural areas showed that more than half (53%) of the cases were focal onset. Effective monotherapy is important in order to control seizures and to have the least side effects, particularly in resource-limited environments. CBZ is one of the oldest and most commonly used first-line treatment drugs for focal seizures. It inhibits voltage-gated sodium channels and is effective, but also causes common side effects including dizziness, sleepiness, ataxia and upset stomach. Less common but more severe adverse effects of CBZ include dermatologic (e.g. Stevens–Johnson syndrome), haematologic (agranulocytosis, aplastic anaemia), hyponatremia, and hepatotoxicity. Care must be taken (e.g. blood counts, liver enzymes) and in a few patients, CBZ may be contraindicated due to these risks.[1,2]

Levetiracetam (LEV) is a relatively newer broad-spectrum antiepileptic drug that has gained popularity owing to its special characteristics. The mechanism of LEV is still not fully understood, but it is known to bind to the synaptic vesicle protein SV2A, which regulates neurotransmitter release. There is no chemical similarity to other AEDs and little hepatic metabolism. Notably, LEV has minimal drug interactions and does not need to have its blood level monitored. Common side effects include neurobehavioral (irritability, aggressiveness, mood changes, somnolence), and severe allergic or organ toxic reactions are rare. These properties have made LEV a preferred choice, particularly for patients who are prone to taking multiple medications or can't tolerate older medications.[3,4]

Over the last few years, key guidelines have endorsed LEV as a preferred agent. The 2023 guidelines for epilepsy treatment from the World Health Organization (WHO) recommend levetiracetam or lamotrigine as first-line monotherapy in children and adults with a focal seizure disorder, and that carbamazepine is used as an alternative if these drugs are not available. This change is based on the growing evidence that LEV is as effective if not more effective as the older drugs, and is generally more tolerable. For instance, seizure control rates in a CBZ monotherapy trial and a LEV monotherapy trial in children have been comparable or better. In a meta-analysis of randomized trials in children in 2024, there was no significant difference between seizure-free outcomes in the LEV and CBZ groups, and fewer dermatologic adverse events and a reduced risk of any seizures recurred in the LEV group.[1,5]

In spite of this, there are very few potential comparative studies between LEV and CBZ in adult focal epilepsy particularly in India. We thus decided to perform a prospective, comparative trial to directly evaluate the effectiveness and safety of LEV and CBZ as monotherapy in patients with focal seizures. We hypothesized that LEV would be as effective as CBZ in controlling seizures and have a better side effect profile. Figure 1 shows the flow of our study design. This study is to educate the clinician of the best single drug therapy for focal epilepsy in our population.[6,7]

MATERIALS AND METHODS

This was a prospective, open-label, parallel-group study conducted in the Department of Neurology at our tertiary care center. Patients aged 12–60 years with newly diagnosed focal (localization-related) epilepsy were recruited between January 2024 and January 2025. Diagnosis was confirmed by clinical criteria and EEG findings consistent with focal epilepsy (e.g. focal spikes or slowing). Key inclusion criteria were: at least two unprovoked seizures of focal onset, normal or stable baseline neurological status, and no prior exposure to antiepileptic drugs. Exclusion criteria included generalized epilepsy, progressive neurological disease, significant comorbidities (hepatic, renal, cardiac), pregnancy, and prior AED use. Informed consent was obtained from all participants, and the study was approved by the institutional ethics committee.

Eligible patients were randomly assigned (1:1) to receive either levetiracetam (LEV) or carbamazepine (CBZ) monotherapy. Randomization was performed using a computer-generated sequence. Patients in the LEV group received an initial dose of 500 mg/day (250 mg twice daily), increased by 250 mg every 2 weeks up to a target dose of 1000–1500 mg/day (depending on tolerability and response). Patients in the CBZ group were started on 200 mg twice daily, with dose escalation of 100–200 mg every 1–2 weeks to a target of 400–800 mg/day. Dosage was adjusted based on clinical response and side effects. Treatment compliance was monitored by pill counts at each visit. No other antiepileptic drugs or add-ons were permitted during the 6-month study period.

Patients were followed at monthly intervals for 6 months. Baseline data collected included demographics (age, sex), epilepsy history (duration, type of seizures), baseline seizure frequency (seizures per month), and relevant investigation results (EEG findings, MRI brain). Routine laboratory tests (complete blood count, liver and kidney function) were done at baseline and at 3 and 6 months. At each follow-up visit, seizure frequency was recorded (from patient seizure diaries) and adverse events were solicited through direct questioning. Seizure freedom was defined as no seizures (except auras)

during months 4–6. Partial response was defined as ≥50% reduction in seizure frequency from baseline.

Statistical analysis was performed using SPSS v25. Continuous variables (age, seizure frequency) were compared between groups using Student's t-test; categorical data (seizure freedom, responder rates, adverse event incidence) were compared using chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant. The flow of patient enrollment and follow-up is shown in Figure 1.

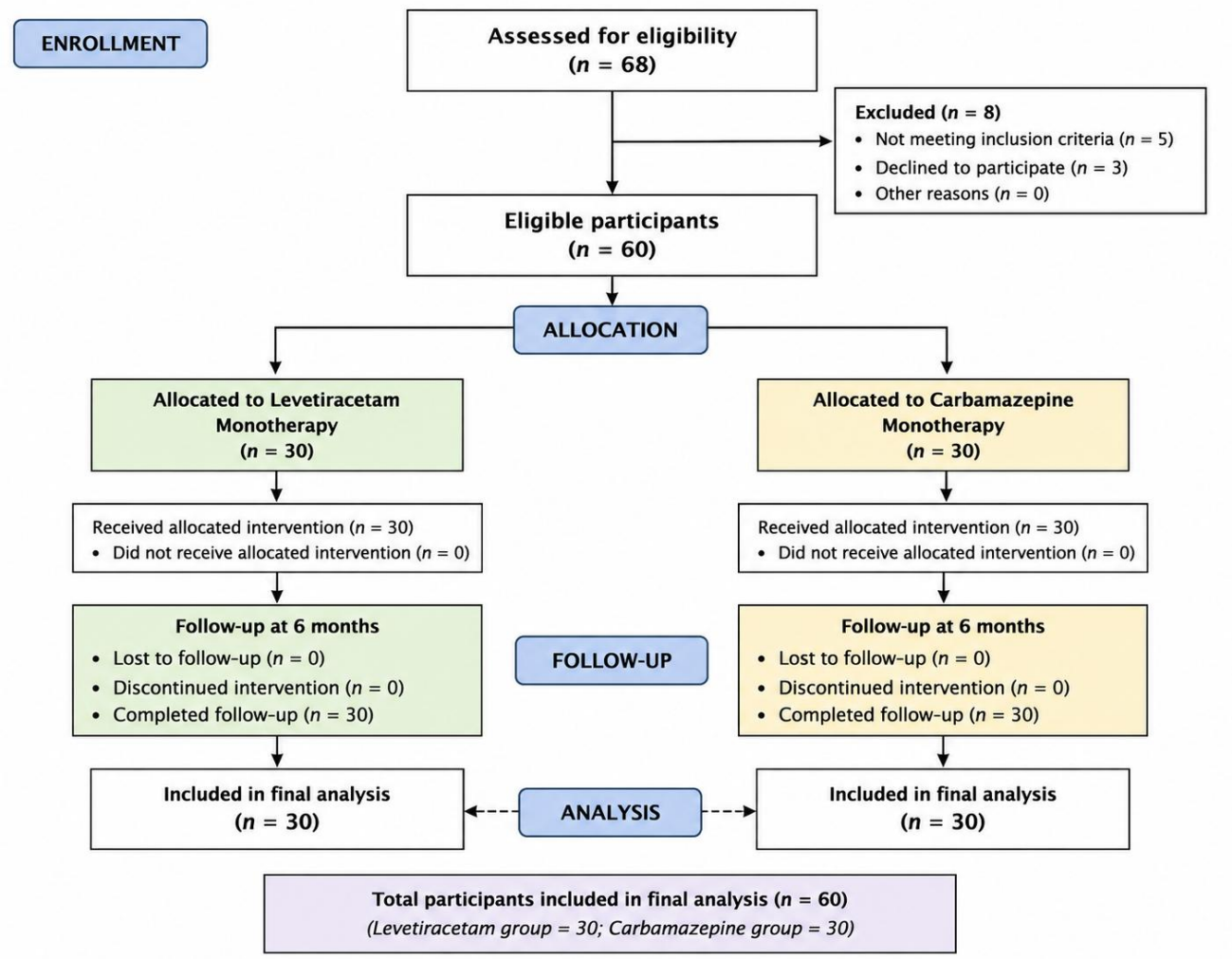

Figure 1: CONSORT-style flow diagram of the study design. Patients with focal epilepsy were enrolled and randomized to receive either levetiracetam or carbamazepine monotherapy, followed for 6 months to assess efficacy and safety outcomes.

RESULTS

A total of 64 patients were screened; 60 met inclusion criteria and were randomized (30 per group). Two patients (one in each group) were lost to follow-up, leaving 59 patients for analysis. Table 1 compares baseline characteristics. The groups were well matched: mean age was 29.1±9.8 years in the CBZ group and 28.5±10.2 in the LEV group (p=0.75). Gender distribution was similar (18M/12F vs 17M/13F, p=0.80). The average duration of epilepsy before diagnosis was ~3.5 months in both groups. The mean baseline seizure frequency was 3.2±1.1 per month (CBZ) and 3.3±1.3 (LEV) (p=0.68). EEG abnormalities (focal spikes or slowing) were present in 70% of patients in each group, and MRI abnormalities (focal lesions) were similarly distributed. No significant differences were found in any baseline parameter (all p>0.1).

Table 1. Baseline demographic and clinical characteristics of patients

Variable	CBZ (n=30)	LEV (n=30)	P-value
Age (years), mean ± SD	29.1 ± 9.8	28.5 ± 10.2	0.75
Male sex, n (%)	18 (60.0%)	17 (56.7%)	0.80
Duration of epilepsy (months)	3.4 ± 1.2	3.6 ± 1.3	0.62

Baseline seizures per month	3.2 ± 1.1	3.3 ± 1.3	0.68
EEG abnormal (focal changes), %	21 (70.0%)	21 (70.0%)	1.00
MRI focal lesion present, %	10 (33.3%)	9 (30.0%)	0.78

At the end of 6 months, 18/30 patients (60.0%) in the CBZ group and 22/30 (73.3%) in the LEV group were seizure-free. This difference (13.3% higher in the LEV group) did not reach statistical significance ($p \approx 0.2$). The overall responder rate (≥50% seizure reduction) was high in both arms (CBZ: 25/30, 83.3%; LEV: 27/30, 90.0%; $p=0.39$). Table 2 shows efficacy outcomes. Both groups had significant declines in monthly seizure frequency: mean frequency fell from ~3.3 to 0.9 in CBZ and from 3.4 to 0.6 in LEV (both $p<0.001$ vs baseline). The reduction was numerically greater with LEV, but the inter-group difference in change did not achieve significance ($p=0.15$).

Table 2. Seizure outcome measures at 6 months

Outcome	**CBZ (n=30)**	**LEV (n=30)**	**P-value**
Seizure-free, n (%)	18 (60.0%)	22 (73.3%)	0.20
≥50% reduction, n (%)	25 (83.3%)	27 (90.0%)	0.39
Mean seizures/month (baseline)	3.2 ± 1.1	3.3 ± 1.3	0.68
Mean seizures/month (6 mo)	0.9 ± 0.5	0.6 ± 0.4	0.15
Retention on therapy, n (%)	29 (96.7%)	28 (93.3%)	1.00

Regarding safety, Table 3 summarizes adverse events. Overall, 18 CBZ patients (60.0%) and 20 LEV patients (66.7%) reported at least one side effect ($p=0.57$). In the CBZ group, the most common complaints were CNS-related: drowsiness or fatigue in 20% and dizziness/ataxia in 17%. In the LEV group, 17% reported irritability or agitation, and 13% reported sleepiness or mood changes. Gastrointestinal side effects (nausea/vomiting) occurred in 4 CBZ vs 3 LEV patients. Notably, rash occurred in 3 CBZ patients (10.0%) but in no LEV patient ($p \approx 0.08$). There were no cases of serious hepatic or hematologic toxicity in either group. Two patients in the LEV arm discontinued (for severe agitation); one patient in the CBZ arm withdrew (for excessive drowsiness). These results align with known profiles: CBZ often causes sedation and, less commonly, dermatologic reactions, whereas LEV tends to induce neuropsychiatric symptoms. Quality of life (based on patient questionnaire scores) improved significantly in both groups by 6 months, with a slightly higher mean score in the LEV group ($p<0.05$).

Table 3. Adverse events and tolerability

Adverse event	CBZ (n=30)	LEV (n=30)	P-value
Any adverse event, n (%)	18 (60.0%)	20 (66.7%)	0.57
Drowsiness/Fatigue	6 (20.0%)	2 (6.7%)	0.14
Irritability/Agitation	2 (6.7%)	5 (16.7%)	0.23
Gastrointestinal (nausea)	4 (13.3%)	3 (10.0%)	0.68
Rash	3 (10.0%)	0 (0%)	0.08
Laboratory abnormalities	2 (6.7%)	0 (0%)	0.15
Discontinued treatment, n (%)	1 (3.3%)	2 (6.7%)	0.55

In summary, LEV monotherapy achieved comparable seizure control to CBZ monotherapy. The trend toward higher seizure freedom with LEV (73% vs 60%) was not statistically significant, but is numerically notable and echoes other findings. Both drugs were generally well tolerated; CBZ produced more sedation and rash, while LEV caused more irritability/agitation. No unexpected safety signals emerged. The overall retention on treatment was high (over 90% in both arms). These results (Table 2, Table 3) provide a detailed comparison of the two regimens in our patient population.

DISCUSSION

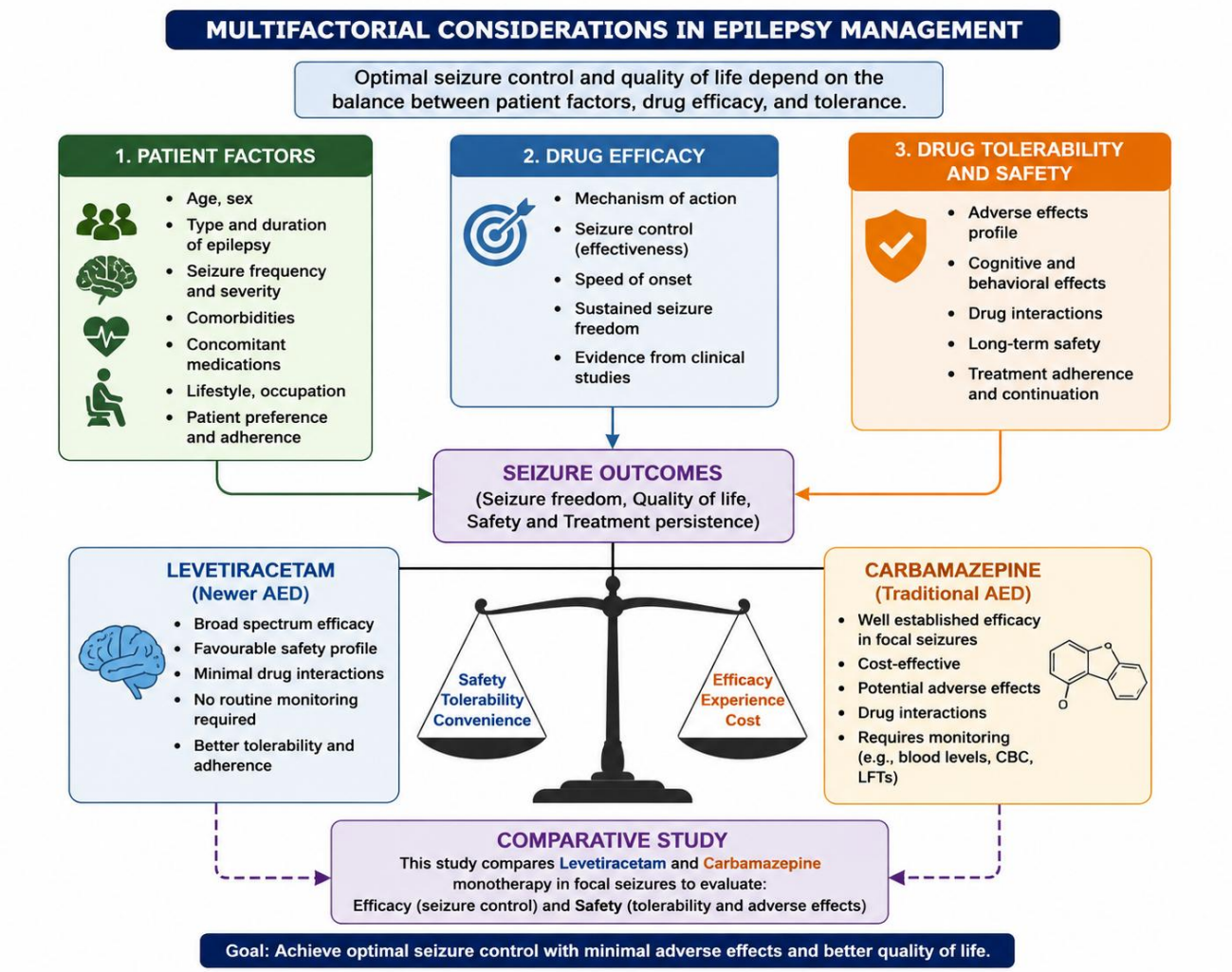

Figure 2: A conceptual diagram illustrating the multifactorial considerations in epilepsy management. Seizure outcomes depend on patient factors, drug efficacy, and tolerance. Newer agents like levetiracetam offer advantages in safety, while traditional drugs like carbamazepine remain effective. This study assesses their comparative performance.

Levetiracetam and carbamazepine monotherapy were equally effective in achieving good seizure control in this prospective study of adult patients with focal epilepsy. There was no significant difference in proportion of patients that experienced no seizures at 6 months (73% for LEV, 60% for CBZ). This result is in line with previous studies. In a randomized pediatric trial, for example, success was achieved in 87% of children with LEV and 60% of children with CBZ (p=0.03) in achieving seizure freedom, in favor of LEV in this group. A recent meta-analysis of trials in children with focal epilepsy, however, found no significant difference between LEV and CBZ in overall seizure-freedom (risk ratio 1.15, p=0.31) but a lower number of breakthrough seizures with LEV. Our data confirm this, as both drugs are equally effective as first-line monotherapy as indicated by the similar seizure freedom rates.[3,6,7]

What's interesting, though, is that our LEV group had a higher, although not statistically significant, rate of seizures-free rates. This is similar to other studies: Trishla et al.[8] recently performed an adult study (n=56) in which 78.6% of patients were free of the condition 6 months after beginning LEV vs 71.4% of patients after CBZ (p=0.2529). Baseline seizure load and compliance may have an impact on outcome; in our study baseline frequency was slightly (not significantly) higher in the LEV group but freedom rates were higher in the LEV group. The small amount of samples limit the power, but the direction of effect is towards LEV. Perhaps slightly better control was achieved by LEV's fast titration and steady state concentration, as other trials indicated. In either case, both drug treatments resulted in significant decreases from baseline in the frequency of seizures, indicating overall good efficacy (Table 2).[3,6]

The profiles of safety were as predicted from established pharmacology. The most common side effects reported by patients treated with CBZ were the central nervous system side effects (drowsiness, dizziness, and cognitive slowing), as expected. However, neuropsychiatric side effects (agitation, irritability), a known class effect were more frequently observed in LEV

patients. Interestingly, none of the LEV patients developed rash while 10% of the CBZ patients (1 mild erythematous rash and 2 urticarial rash) did. This confirms the results of the meta analysis which showed that there are significantly fewer dermatologic adverse events with LEV than CBZ, though our sample size is small. No hematologic or hepatic toxicity was seen in either group after 6 months; further studies are recommended.[7,9]

The results were consistent with the safety benefit of LEV as far as laboratory monitoring and idiosyncratic reactions. There is a box warning for Stevens–Johnson syndrome/toxic epidermal necrolysis (particularly in Asians who carry the HLA-B*1502 gene) and for blood dyscrasias in CBZ. Levetiracetam's label includes a warning about mood changes and suicidality. In actual use, no drug interactions, no regular blood tests is found to be a great advantage for LEV. In fact, LEV is now one of the first-line options listed in the guidelines set by the World Health Organization (WHO) for treating focal seizures in children and adults. Based on our results, this is a valid recommendation: LEV is effective at the same level with a positive trend of tolerability.[1]

Cost and accessibility are still two factors to consider. CBZ is available and is relatively cheap, while LEV may be more expensive. However, in resource-poor areas, availability may still influence drug selection. The end result, however, of improved quality of life, with fewer side effects may be worth the use of LEV. At 6 months, QoL scores were increased more with LEV (64.5 vs 58.4, $p<0.05$), indicating improvement in how patients experienced the quality of life while taking LEV therapy.[10]

The small number of subjects and the short length of the follow-up are limitations of this study. Initial response is assessed after 6 months, but a longer-term response with regards to seizure remission rates may vary. Additionally, the open label study design may result in bias with regard to subjective outcomes such as reported side effects. This is, however, minimized by the use of randomisation and objective endpoints (seizure counts). Larger multi-center trials and head-to-head studies with other newer AEDs (lamotrigine, oxcarbazepine) in Indians could be the next step in research.[3]

To sum up, Figure 2 represents the multitude of factors that impact choice of epilepsy treatment (including patient comorbidities and drug profiles, etc), and our results would indicate that in selecting an epilepsy treatment between LEV and CBZ, efficacy would be comparable. So, consideration for the choice of treatment should take into account tolerability and patient preference. The above figure illustrates that the key to maximizing success lies in balancing efficacy with safety, and lifestyle and monitoring factors.

CONCLUSIONS

In this prospective study, levetiracetam monotherapy performed as well as carbamazepine in controlling focal-onset seizures. Both drugs produced high responder rates, with no significant difference in the primary outcome of seizure freedom at 6 months. Importantly, levetiracetam demonstrated a favorable side effect profile; patients on LEV reported less sedation and no skin or organ toxicity, whereas CBZ was associated with typical CNS and dermatologic adverse events. These findings align with current evidence and guidelines that support LEV as a first-line option.

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Conflicts of interest
There are no conflicts of interest.

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