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RESEARCH ARTICLE

# Prescribing Pattern of Levetiracetam in Epilepsy Patients: A Cross-Sectional Study in a Tertiary Care Centre in Manipur

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## Abstract

**Objective:** The objective is to shed light on the prescribing pattern of levetiracetam, a newer antiepileptic drug, in the treatment of different types of epilepsy. **Methods:** A record-based cross-sectional study of epilepsy patients who reported to the Therapeutic Drug Monitoring Unit in the Department of Pharmacology, Regional Institute of Medical Sciences, Manipur, was conducted. Case records of patients receiving levetiracetam and reporting from January 2017 to December 2020 were included. The patient's age, gender, and weight; clinical diagnosis; levetiracetam dose; and other co-administered AEDs were all examined. **Findings:** Of the 17 cases, the majority of the patients were adults, and 52.9% were males. The patients' average body weight (kg) was 49.8 $\pm$ 9.4. Generalised tonic-clonic seizures (GTCS) constituted the majority of the cases (47.1%), followed by simple partial seizures, complex partial seizures (23.5% of each), and absence seizures (5.9%). 70.11% of the cases received LEV monotherapy, while the remaining cases were prescribed combination therapy**.** LEV alone was prescribed in 87.5% of GTCS cases. The median daily dose of LEV was 1000 mg (IQR-625). **Novelty :** The observation that levetiracetam alone is prescribed in the majority of GTCS cases, the commonest type of epilepsy, is an eye-opener for another new monotherapy option for GTCS.

**Keywords:** Prescribing pattern; Levetiracetam; Antiepileptic; Epilepsy; Monotherapy

## 1 Introduction

Despite receiving treatment with a variety of antiepileptic drugs (AEDs), either alone or in combination, about one-third of epilepsy patients continue to experience seizures.

The availability of newer agents, together with established drugs, has broadened the choices for the treatment of patients with focal or generalised epilepsy[1]. The favourable pharmacokinetic profiles and lower interaction rates make the newer antiepileptic drugs better tolerated than the older ones[2].

Levetiracetam [(S)-$\alpha$-ethyl-2-oxo-1-pyrrolidine acetamide] is a newer antiepileptic drug. The exact mechanism of the antiepileptic effect of levetiracetam remains unclear. However, the modulation of synaptic neurotransmitter release through binding to synaptic vesicle protein 2A (SV2A) in the brain is a key driver of its antiepileptic action. Levetiracetam binding to SV2A may modify glutamate and GABA release by affecting vesicular function, which in turn may have an impact on neuronal excitability. It also prevents $Ca^{2+}$ release from intracellular stores and inhibits N-type $Ca^{2+}$ channels[3]. Levetiracetam is quickly and almost completely absorbed after oral administration, reaching its peak concentration after 1-2 hours. The volume of distribution of LEV is 0.5–0.7 L/kg. Approximately 24% of a levetiracetam dose is metabolised by hydrolysis, primarily in the blood, and 66% is excreted in urine unmetabolized[4]. The protein binding is negligible, posing no risk of competition with other drugs for binding sites. The plasma half-life is 6-8 hours, which may be prolonged in older patients. Levetiracetam has no known significant interactions with other antiepileptic drugs because it neither induces hepatic microsomal enzymes nor is a high-affinity substrate for these enzymes. Levetiracetam is reported to be effective as adjunctive therapy for refractory partial-onset seizures, and primary generalised tonic-clonic seizures. Nowadays, this drug has been approved for adjunctive treatment of generalised onset tonic-clonic, focal-onset (partial), and myoclonic seizures in adults and children as young as 4 years old[3]. There is strong evidence that levetiracetam can be used as an alternative drug to the established first-line drugs for partial and generalised seizures. It can be the first-line therapy for female epilepsy patients of childbearing potential[5].

The recent literature shows that a number of studies have been published on the patterns of use of antiepileptic drugs in epilepsy patients in India[6–8]. These studies focus mainly on the prescribing trends of AEDs as a whole rather than the use of individual drug(s) for distinct epilepsy types. The report on the recent study of LEV in India is also related to its use in pregnancy and mentions the use of this drug as monotherapy or in combination with other AEDs without specifying the epilepsy types[9]. In the Indian population, it is obvious that information on the recent trend in the pattern of LEV prescription with regard to the various epilepsy types is scarce. Therefore, this study was planned to highlight the prescribing patterns of levetiracetam in various epilepsy types, based on a small study done in one of the premier medical institutes in Manipur, a state in northeast India.

## 2 Methodology

The study was conducted after the approval of the Institutional Research Ethics Board. A record-based cross-sectional study of epilepsy patients who attended the Therapeutic Drug Monitoring (TDM) unit for AEDs in the Department of Pharmacology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur was conducted. All the case files of the epilepsy patients reported during the period from January 2017 to December, 2020 were checked. The case records of all the patients receiving levetiracetam alone or in combination with other antiepileptic drugs were included in the study.

The demographic profiles of the patients, such as age, sex and weight, clinical diagnosis, levetiracetam dose, and other co-administered AEDs were recorded in a predesigned form. The collected data were entered into IBM SPSS version 25, and descriptive statistics such as percentage, mean, median, standard deviation, and interquartile range were used to represent the data. Fisher's exact test was used to see association between the seizure types and drug therapy used. P value $\leq 0.05$ was considered significant.

## 3 Results and Discussion

A total of 17 case records were enrolled in the study. The most common age group reported was between 25 and 65 years, followed by 14 to 24 and below 14. In 11.7% of the cases, the patients were children (<14 years). The mean age of the patients was 27.6 $\pm$ 14.5. With relation to gender distribution, it was observed that 52.9% were males and 47.1% were females. The average body weight (kg) of the patients was 49.8 $\pm$ 9.4. Generalised tonic-clonic seizures constituted the majority of the cases (47.1%), followed by simple partial seizures and complex partial seizures (23.5% of each type). 5.9% of the cases had absence seizures .

The majority of the cases (70.11%) in this study received monotherapy with LEV, and the remaining cases were prescribed combination therapy of other antiepileptic drug/s with LEV. Of the combination therapies, the combination of LEV with OCB made up 11.9% of the total, followed by the combinations of LEV with CLO (5.9%), with OCB (5.9%), with OCB and DVP (5.9%), and with CBZ and PHT (5.9%). The total daily dose of LEV reflected a median daily dose of 1000 mg (IQR-625). The mean dose of LEV in mg/kg body weight was 21.1 $\pm$ 5.6.

**Table 1.** Demographic profiles and types of epilepsy (N = 17)

| Patient profile | Statistic | Value |
|---|---|---|
| Gender | | |
| Male | n (%) | 9(52.9) |
| Female | n (%) | 8(47.1) |
| Age in years | | |
| < 14 | n (%) | 2(11.7) |
| 15 - 24 | n (%) | 7(41.2) |
| 25 - 65 | n (%) | 8(47.1) |
| > 65 | n (%) | 0 |
| Weight | Mean ± SD | 49.8 ± 9.4 |
| Seizure type | | |
| GTCS | n (%) | 8(47.1) |
| | n (%) | 4(23.5) |
| CPS | n (%) | 4(23.5) |
| Absence seizure | n (%) | 1(5.9) |

Note: SD - Standard deviation, GCTS -Generalized tonic clonic seizure, SPS - Simple partial seizure, CPS - Complexpartial seizure.

**Table 2.** Proportion of LEValone and with other AEDs, and the dose prescribed

| Antiepileptic drug | Statistic | Value |
|---|---|---|
| LEV | n (%) | 12(70.6) |
| LEV+CLO | n (%) | 1(5.9) |
| LEV+OCB | n (%) | 2(11.9) |
| LEV + OCB + DVP | n (%) | 1(5.9) |
| LEV + CBZ + PHT | n (%) | 1(5.9) |
| LEV - mg/day per oral | Median(IQR) | 1000(625) |
| LEV- mg/kg body weight | Mean ± SD | 21.1 ± 5.6 |

Note: SD - Standarddeviation, IQR - Interquartile range; LEV- Levetiracetam, CLO - Clobazam, OCB -Oxcarbazepine, CBZ - Carbamazepine, DVP-Divalproex, PHT - Phenytoin.

LEV alone was prescribed in 87.5% of all cases of GTCS, and 12.5% were given combination therapy. In the other types of epilepsies, which included SPS, CPS, and absence seizures, monotherapy with LEV was advised in 55.6% of the patients, while combination treatment of LEV with other AEDs was prescribed in 44.4%. There was no significant relation between the types of the seizures, and the prescribed medication i.e. LEV alone and in combination with other AEDs.

**Table 3.** LEV alone and withother AEDs in different seizure types

| Seizure type | LEV (%) | LEV with other AED/s (%) | Total | P value* |
|---|---|---|---|---|
| GTCS | 7(87.5) | 1(12.5) | 8 | 0.294 |
| Others | 5 (55.6) | 4 (44.4) | 9 | |

Note: *Fisher's exact test. Other seizure types represented SPS or CPS orabsence seizure.
Other AED/s included CLO or OCB or (OCB +DVP) or (CBZ + PHT).

In our study, GTCS is the most common type reported and male patients predominated females. These observations are in agreement with reports of various workers in India[10–12]. The mean age of 27.6 ± 14.5 years in this study is higher than the reported figures of 21.9 years (range 2-77)[10] and 21.64 ± 10.46[11]. The sex distribution differs from that of Vyas N et al., who found female predominance[13].

Levetiracetam is prescribed in the treatment of different seizure types, such as GTCS, SPS, CPS, and absence seizures, with a median dose which is within the accepted therapeutic range. The prescriptions indicate the use of LEV either as monotherapy or in combination with other antiepileptic drugs. LEV has been shown to be an effective adjunctive treatment for generalized-onset tonic-clonic, focal-onset (partial), and myoclonic seizures in the literature[3]. In a review of recent clinical evidence,

levetiracetam is shown to be equally effective as carbamazepine, clobazam, and valproic acid in the treatment of various types of epileptic seizures, but with greater tolerability than carbamazepine. The treatment of newly developed focal epilepsy may involve the use of levetiracetam as a monotherapy, and it may be a first-choice second-line AED for benzodiazepine resistance status epilepticus with efficacy comparable to known older AEDs [14].

It is accepted that in comparison with polytherapy, monotherapy has obvious advantages, such as ease of adherence to the treatment plan, less cost, fewer drug interactions, and consequently fewer adverse effects. However, polytherapy has an unquestionable role if monotherapy fails [15]. In recent studies carried out in India, levetiracetam was the most commonly prescribed AED [12,13,16]. In our study, GTCS was the most common epilepsy type treated with levetiracetam monotherapy. For other types of epilepsies, such as SPS, CPS, and absence seizures, levetiracetam was co-prescribed with other antiepileptics.

In Our study the mean dose/kg body weight/day of LEV is 21.1± 5.6 while some of the reports recorded mean dose of LEV for seizure control as 27.9 ± 5.4 mg/kg/day [17] and 60 mg/kg/day [18]. When selecting an epileptic medication, a number of variables are typically taken into account, such as seizure type, tolerability, efficacy, patient characteristics like age and gender, and affordability [2]. The dose variations seen in the different studies might be because of the number of variable factors mentioned above.

## 4 Conclusion

The present study throws some light on the prescribing pattern of levetiracetam, a newer antiepileptic drug with a good safety profile and efficacy. Our observation shows LEV is prescribed mostly as monotherapy in generalised tonic-clonic seizures. It is a fact that studies on the prescription patterns of medications play a key role in helping to understand, interpret, and improve prescribing, which will ultimately facilitate the rational use of drugs. Well-planned, large studies on the prescribing pattern of the drug and randomised controlled studies of levetiracetam versus other AED(s) or levetiracetam in combination with other antiepileptics will provide a decisive understanding of its status in epilepsy treatment. As our study is a record-based cross-sectional study with a small sample size, and the restraint on data collection, the results may not be generalisable. The lack of information on the adverse effects, patient compliance, and efficacy of satisfactory seizure control with levetiracetam are notable limitations of this study.

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