MODULES ON EPILEPSY

MODULE V

Understanding Prescribing Pattern of F Levetiracetam in Seizure Management

CONTENT

Prescribing Patterns of Levetiracetam in Various Epilepsy Types

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 generalized epilepsy. The favorable pharmacokinetic profiles and lower interaction rates make the newer antiepileptic drugs better tolerated than the older ones.

Drug Profile

Levetiracetam [(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide] is one such newer antiepileptic drug. The exact mechanism of its antiepileptic effect remains unclear, but it is known to modulate synaptic neurotransmitter release through binding to synaptic vesicle protein 2A (SV2A) in the brain, which is a key driver of its action. Levetiracetam's binding to SV2A may modify glutamate and GABA release by affecting vesicular function, thereby impacting neuronal excitability. Additionally, it prevents Ca2+ release from intracellular stores and inhibits N-type Ca2+ channel.

Levetiracetam is quickly and almost completely absorbed after oral administration, reaching its peak concentration after 1-2 hours. The volume of distribution is 0.5–0.7 L/kg. Approximately 24% of a levetiracetam dose is metabolized by hydrolysis, primarily in the blood, and 66% is excreted in urine unmetabolized. Its negligible protein binding poses no risk of competition with other drugs for binding sites, and its plasma half-life is 6-8 hours, which may be prolonged in older patients. Levetiracetam has no 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 generalized tonic-clonic seizures. It is now approved for adjunctive treatment of generalized onset tonic-clonic, focal-onset (partial), and myoclonic seizures in adults and children as young as 4 years old. There is strong evidence that levetiracetam can be used as an alternative drug to the established first-line drugs for partial and generalized seizures and can be the first-line therapy for female epilepsy patients of childbearing potential.

Recent literature shows that several studies have been published on the patterns of AED use in epilepsy patients in India. These studies focus mainly on the prescribing trends of AEDs as a whole rather than the use of individual drugs for distinct epilepsy types. The report on the recent study of levetiracetam in India is also related to its use in pregnancy and mentions its use as monotherapy or in combination with other AEDs without specifying the epilepsy types. In the Indian population, it is evident that information on the recent trend in the pattern of levetiracetam prescription with regard to the various epilepsy types is scarce.

Methodology

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

Data Collection

The demographic profiles of the patients, such as age, sex, weight, clinical diagnosis, levetiracetam dose, and other coadministered AEDs, were recorded in a predesigned form.

Data Analysis

The collected data were entered into IBM SPSS version 25. 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 examine the association between seizure types and the drug therapy used. A p-value ≤ 0.05 was considered significant.

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 years, and below 14 years. In 11.7% of the cases, the patients were children (below 14 years). The mean age of the patients was 27.6 ± 14.5 years. Regarding gender distribution, 52.9% were males and 47.1% were females. The average body weight of the patients was 49.8 ± 9.4 kg.

Seizure Types

- Generalized tonic-clonic seizures constituted the majority of the cases (47.1%).

- Simple partial seizures and complex partial seizures each accounted for 23.5% of the cases.

- Absence seizures were observed in 5.9% of the cases.

Treatment Patterns

Monotherapy: The majority of the cases (70.11%) received levetiracetam (LEV) as monotherapy.

Combination Therapy: The remaining cases were prescribed combination therapy with other AEDs alongside LEV. The combinations included:

- LEV with oxcarbazepine (OCB): 11.9%
- LEV with clonazepam (CLO): 5.9%
- LEV with OCB and divalproex (DVP): 5.9%
- LEV with carbamazepine (CBZ) and phenytoin (PHT): 5.9%

Dosage

- The total daily dose of LEV had a median of 1000 mg (IQR = 625).
- The mean dose of LEV in mg/kg body weight was 21.1 ± 5.6 mg/kg

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.

MONOTHERAPY VS. COMBINATION THERAPY

Generalized Tonic-Clonic Seizures (GTCS): LEV alone was prescribed in 87.5% of GTCS cases, with 12.5% receiving combination therapy.

Other Seizure Types (Simple Partial Seizures (SPS), Complex Partial Seizures (CPS), Absence Seizures): Monotherapy with LEV was advised in 55.6% of these patients, while 44.4% received combination treatment with other AEDs.

There was no significant relationship between seizure types and the prescribed medication (LEV alone or in combination with other AEDs).

Observations and Comparisons

In our study, GTCS was the most common type of epilepsy reported, and male patients predominated over females. These findings align with reports from various studies in India. The mean age of 27.6 ± 14.5 years in this study is higher than the reported figures of 21.9 years and 21.64 ± 10.46 years in other studies. The sex distribution differs from that of Vyas N et al., who found a female predominance.

Levetiracetam is prescribed for various seizure types, including GTCS, SPS, CPS, and absence seizures, with a median dose within the accepted therapeutic range. The prescriptions indicate the use of LEV either as monotherapy or in combination with other AEDs. Levetiracetam has been shown to be an effective adjunctive treatment for generalized-onset tonic-clonic, focal-onset (partial), and myoclonic seizures. Clinical evidence suggests that levetiracetam is as effective as carbamazepine, clobazam, and valproic acid in treating various epileptic seizures but has greater tolerability than carbamazepine.

Advantages of Monotherapy vs. Polytherapy:

- Monotherapy has advantages such as ease of adherence, lower cost, fewer drug interactions, and consequently fewer adverse effects.

- Polytherapy is essential when monotherapy fails.

In recent studies in India, levetiracetam was the most commonly prescribed AED. Our study also found GTCS to be the most common epilepsy type treated with levetiracetam monotherapy. For other epilepsy types, such as SPS, CPS, and absence seizures, levetiracetam was often co-prescribed with other antiepileptics.

Dosage Comparisons

In our study, the mean dose of LEV was 21.1 ± 5.6 mg/kg/day. Some other reports recorded mean doses of LEV for seizure control as 27.9 ± 5.4 mg/kg/day and 60 mg/kg/day. When selecting an epileptic medication, several variables are typically considered, such as seizure type, tolerability, efficacy, patient characteristics like age and gender, and affordability. The dose variations seen in different studies might be due to these variable factors.

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).

The present study provides insight into the prescribing patterns of levetiracetam, a newer antiepileptic drug known for its good safety profile and efficacy. Our observations indicate that levetiracetam is predominantly prescribed as monotherapy for generalized tonic-clonic seizures (GTCS).

Studies on the prescription patterns of medications are crucial as they help to understand, interpret, and improve prescribing practices. This ultimately facilitates the rational use of drugs. Comprehensive, well-planned studies on the prescribing patterns of levetiracetam, as well as randomized controlled trials comparing levetiracetam with other AEDs or in combination with other antiepileptics, are necessary to gain a decisive understanding of its status in epilepsy treatment.

Further large-scale, randomized controlled studies are needed to better understand the role of levetiracetam in epilepsy treatment. These studies should focus on its comparative efficacy, safety, and patient outcomes in different epilepsy types.

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REAPPRAISING LEVETIRACETAM IN EPILEPSY TREATMENT: A REVIEW

Levetiracetam (LEV) is one of the most commonly prescribed antiseizure medications (ASMs) worldwide for various epilepsy syndromes and clinical scenarios. Its widespread use is attributed to its favorable pharmacokinetic and tolerability profiles, especially when compared with first-generation ASMs such as valproate (VPA), carbamazepine (CBZ), and phenytoin (PHE). However, its potential overuse in clinical practice may overshadow other ASMs that might be more appropriate in certain scenarios.

LEV is recognized for its broad application across multiple epilepsy types due to its favorable safety and tolerability. Despite this, studies like the SANAD II trial recommend VPA for genetic or idiopathic generalized epilepsies (GGE/IGE) and lamotrigine (LTG) for focal epilepsies due to their increased efficacy and tolerability compared to LEV. Additionally, the KOMET Trial showed that LEV did not demonstrate superiority over VPA and CBZ in patients with newly diagnosed focal or generalized seizures. These findings suggest that the broad-spectrum approach of LEV might be less optimal than more targeted therapies.

Mechanism of action

LEV's primary molecular action involves binding to synaptic vesicle protein 2A (SV2A), which stabilizes synaptic vesicles, enhances GABA release in inhibitory synapses, and downregulates glutamate activity in excitatory synapses. This modulation helps equilibrate neurotransmission, contributing to its antiseizure properties. LEV also modulates calcium currents, further supporting its role in seizure control.

Pharmacology

LEV exhibits predictable linear pharmacokinetics with minimal individual variability and almost complete oral bioavailability. It has a low protein-binding rate and is primarily eliminated through renal clearance. Its plasma half-life is 6–8 hours, allowing for twice-a-day dosing. The drug is available in several formulations, including intravenous and extended-release preparations. Typical dosing for adults starts at 500 mg twice a day, with gradual increases up to a maximum of 3000 mg per day.

Side Effects and Interactions

LEV is generally well-tolerated, with no significant effects on cardiac, hepatic, or renal systems. However, neuropsychiatric adverse events (NPAEs), such as irritability, are reported in 20–30% of cases. These effects are not dose-dependent and may be influenced by individual predispositions, including genetic factors. LEV has minimal interactions with other medications, although there are reports of potential interactions with direct oral anticoagulants, which have not been confirmed in clinical settings.

Current Role of LEV

LEV is approved for use in various seizure types, including focal-onset, myoclonic, and generalized tonic-clonic seizures. Despite limited monotherapy approvals, it is widely used off-label, particularly in populations where avoiding the adverse effects of other ASMs is crucial, such as in females of childbearing age and the elderly. LEV is favored for its minimal drug interactions and favorable side effect profile, making it a versatile option in diverse clinical scenarios.

Optimal First-Line ASM Scenarios

Idiopathic Generalized Epilepsies (IGE) in Childbearing-Aged Females Due to VPA's teratogenic risks, LEV is a preferred alternative in females of childbearing age with IGE, particularly in juvenile myoclonic epilepsy (JME), where it shows high response rates.

Myoclonic Syndromes

LEV is effective in treating myoclonic seizures, especially in JME and progressive myoclonic epilepsies (PME). It is considered a suitable alternative to VPA in these cases, avoiding VPA's mitochondrial toxicity.

Photosensitive Epilepsies

LEV has demonstrated efficacy in suppressing photic-induced seizures, making it a valuable option for conditions like epilepsy with eyelid myoclonia and photosensitive occipital lobe epilepsy.

LEV's broad application and favorable profile make it a cornerstone in epilepsy treatment. However, its potential overuse highlights the need for precision in therapeutic approaches, tailoring treatment to individual patient needs and specific epilepsy syndromes. Further research and well-designed clinical trials are essential to optimize its use and establish its place among other ASMs in the evolving landscape of epilepsy management.

Precision Use of Levetiracetam in Epilepsy Syndromes

Levetiracetam (LEV) is a widely prescribed antiseizure medication (ASM) due to its favorable pharmacokinetic and tolerability profiles. However, evidence suggests that its use may not always be optimal compared to other ASMs in certain clinical scenarios. This review explores the precise application of LEV in various epilepsy syndromes and clinical conditions.

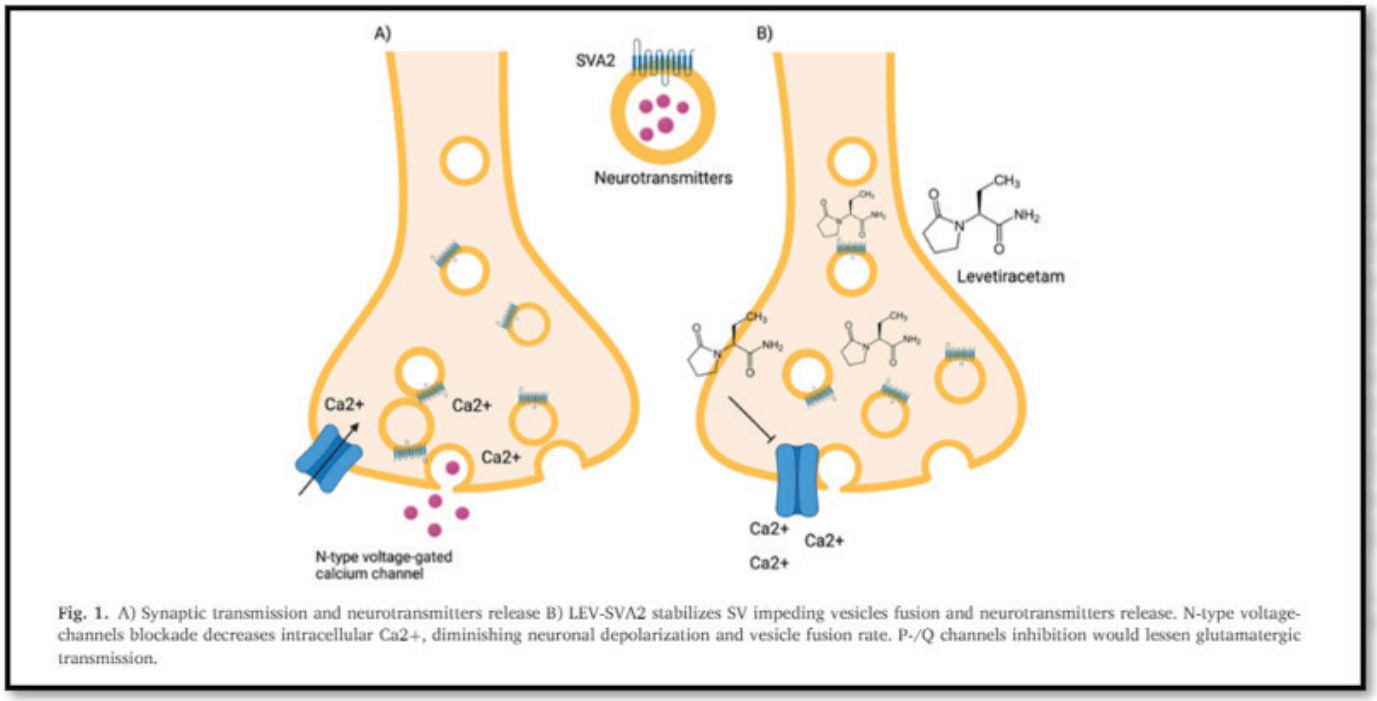

Fig. 1. A) Synaptic transmission and neurotransmitters release B) LEV-SVA2 stabilizes SV impeding vesicles fusion and neurotransmitters release. N-type voltage-channels blockade decreases intracellular Ca2+, diminishing neuronal depolarization and vesicle fusion rate. P-/Q channels inhibition would lessen glutamatergic transmission.

PCDH19 Clustering Epilepsy

Seizures in PCDH19 clustering epilepsy or PCDH19-related epilepsy (PCDH19-RE) are highly refractory. However, therapy with LEV has significantly increased the overall responder rate in this condition. Sadleir et al. reported that more than 70% of patients on LEV achieved seizure freedom within the first few years, before the natural stabilization of the disease. These clinical outcomes extend to cognitive and behavioral performance, underscoring the importance of early diagnosis and distinction from Dravet syndrome, where LEV is less effective.

STXBP1 Developmental and Epileptic Encephalopathy

Patients with pathogenic variants in STXBP1 exhibit early refractory seizures and progressive developmental delay. LEV might play a strategic role in reducing enhanced neurotransmitter release. A multicenter observational study supported LEV's effectiveness in decreasing seizure burden in STXBP1-related developmental and epileptic encephalopathy (STXBP1-DEE), although its impact on cognitive function is negligible.

Down Syndrome

The incidence of epilepsy increases with age in patients with Down syndrome. LEV has shown efficacy in treating late generalized myoclonic seizures, a distinct phenotype of Down syndrome-related epilepsy linked to cognitive decline. In some cases, LEV was more effective than VPA, with patients achieving seizure freedom after VPA failure. Slow titration and careful monitoring of psychiatric and behavioral adverse events are recommended.

Elderly Population and Alzheimer's Disease

The selection of ASMs for the elderly must consider effectiveness, age-related pharmacokinetic changes, tolerance, and comorbidities. LEV is appropriate for this population, demonstrating similar effectiveness to other therapies in late-onset epilepsy with longer retention rates. In Alzheimer's disease (AD) patients, LEV reduces epileptiform activity and is associated with improved cognitive performance, unlike other ASMs such as PHE or VPA.

Reproductive and Pregnancy Issues

LEV has one of the lowest teratogenicity rates among ASMs, comparable to LTG and similar to healthy mothers in some cohorts. However, children exposed to LEV in the prenatal period may have a slightly increased prevalence of developmental and behavioral comorbidities. LEV is classified by the FDA as category C, indicating that its benefits may outweigh potential risks. LEV and LTG are recommended as first-line ASMs for pregnant females or those planning a pregnancy. Monitoring LEV concentrations during pregnancy is crucial due to pregnancy-induced drops in drug levels.

Debatable First-Line Use of LEV

Absence Epilepsy

Evidence regarding LEV in absence epilepsy (AE) is heterogeneous, with modest results in most cases. LEV lacks activity over T-voltage gated Ca2+ channels and GABAergic action, which are critical in AE pathophysiology. Therefore, LEV is not solidly supported for AE treatment, although it may work for some patients.

Malformations of Cortical Development

Malformations of cortical development (MCDs) are a frequent cause of drug-resistant epilepsy. LEV has shown low responder rates in patients with MCDs and may worsen epilepsy in some cases. This could be due to decreased SV2A expression in cortical dysplasia and other MCDs.

Epilepsy Related to Primary Brain Tumors and Metastasis

LEV is commonly prescribed in oncologic patients due to its pharmacokinetic profile. However, psychiatric comorbidity and LEV-induced neuropsychiatric adverse events (NPAE) may reduce retention rates and quality of life. The effectiveness of LEV in tumors with low SV2A expression, such as low-grade gliomas, is limited, necessitating a careful assessment of its use.

Self-Limiting Childhood Epilepsy Syndromes

LEV is frequently used in self-limited epilepsy with centrotemporal spikes (SeLECTS) and self-limited epilepsy with autonomic seizures (SeLEAS). However, the high rate of comorbid behavioral disorders warrants a careful risk-benefit analysis regarding NPAE.

Certain Genetic Epilepsies

The precision medicine approach in genetic epilepsies requires understanding the exact pathogenic pathways. For example, SCN8A pathogenic variants can lead to worsening when treated with LEV, indicating the need for SCN8A testing in such cases. Synaptopathies also require careful consideration as LEV might not be effective or could be harmful in some cases.

Table 2

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Table 2: **When to consider LEV as first-line?**

- As an alternative to VPA in females with IGE, specifically JME, epilepsy with tonic-clonic seizures alone, or prominent myoclonic seizures.
- In patients with progressive myoclonic epilepsies.
- As an add-on to other ASM in syndromes with photosensitivity traits: EEM, POLE.
- In elderly population with new-onset epilepsy and cognitive impairment, especially if Alzheimer disease is suspected.
- In patients with Down syndrome and late-onset myoclonic epilepsy.
- Early in PCDH19-RE and STXBP1-DEE.
- In pregnant patients with new-onset seizures.
- In status epilepticus as a first-line along with VPA and PHE.

In which scenarios LEV-therapy is debatable as first line?

- In malformations of cortical development.
- In patients with variants in *SCN8A (GoF), PRRT2* and *SV2A*.
- In absence seizures.
- In patients with tumoral epilepsy with concurrent mood disorders or frontal lobe location of lesion.

*Caution if prescribed in patients with a history of psychiatric comorbidities.

AD: Alzheimer Disease, EEM: Epilepsy with eyelid myoclonia, GoF: Gain of function, LEV: Levetiracetam, PCDH19-RE: PCDH19 related-epilepsy, POLE: Photosensitive Occipital Epilepsy, STXBP1-DEE: Syntaxin-binding protein 1-developmental and epileptic encephalopathy.

Status Epilepticus (SE)

LEV is frequently used in SE due to its ease of administration, dosage, and safety. Recent trials have shown no significant differences in efficacy and safety between LEV, VPA, and PHT in SE management. However, LEV's safety profile may benefit specific clinical scenarios.

Seizure Prophylaxis

Seizure prophylaxis in critically ill patients is controversial. Current guidelines recommend against routine antiseizure prophylaxis without clinical or electroencephalographic evidence of seizure activity. LEV is commonly used in primary seizure prevention in neurocritical settings, but evidence supporting its efficacy in these situations is limited.

LEV's broad application in epilepsy treatment highlights the need for precision in therapeutic approaches. Tailoring treatment to individual patient needs and specific epilepsy syndromes is essential for optimizing outcomes. Further research and well-designed clinical trials are necessary to refine LEV's role in the evolving landscape of epilepsy management.

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