

# Perspectives on Epilepsy Management among Indian Clinicians: A Cross Sectional Study

## Research Article

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### Abstract

**Background:** While a majority of patients with epilepsy are able to maintain seizure control with one to two antiepileptic drugs (AEDs), many individuals require adjunctive therapy to achieve long-term remission. Hence, the implications of seizure differ according to the clinicians' awareness about the patient's condition, knowledge about drugs and perspective about epilepsy treatment modalities. The current study aims in assessing the perspective of clinicians in management of epilepsy in India.

**Methodology:** A questionnaire-based cross sectional study was carried out among doctors in the major Indian cities. The study questionnaire included questions on prevalence, diagnosis, co-morbidities, lifestyle, patient's awareness, compliance, and pharmacotherapy. A total of 93 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data.

**Results:** About 84 questionnaire booklets were distributed and 82 clinicians completed questionnaires and were collected personally by the study coordinators through the duration of 4 weeks. The responses reflected on the prevalence pattern of epilepsy in rural and urban India, the pattern of occurrences of generalized and partial seizures. The prescription pattern with levetiracetam and brivaracetam were unveiled as well.

**Conclusion:** Brivaracetam has emerged as a preferred choice, especially for newly diagnosed patients and those who do not respond adequately to levetiracetam. Its perceived advantages, including minimal adverse effects and improved efficacy, make it a valuable addition to the arsenal of antiepileptic drugs.

**Keywords:** Epilepsy; Seizure; Pharmacotherapy; Brivaracetam; Levetiracetam

### Introduction

Epilepsy is one of the most common and disabling neurologic conditions, yet we have an incomplete understanding of the detailed pathophysiology and, thus, treatment rationale for much of epilepsy. "Epilepsy" is the condition of recurrent, unprovoked seizures, where a "seizure" is a paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain [1]. The majority of those with newly recognized epilepsy have many seizures before diagnosis. Often, repetitive symptoms are necessary to establish a diagnosis; moreover, close temporal proximity of sequential seizures may be the reason patients seek medical care [2].

Most of the epilepsy patients reside in developing countries. About 10 million persons with epilepsy are there in India. Many people with active epilepsy do not receive appropriate treatment for their condition, leading to large treatment gap [3]. The pharmacological armamentarium against epilepsy has expanded considerably over the last three decades, and currently includes over 30 different anti-seizure medications. The administration of antiepileptic drugs (AEDs) was the first treatment of epilepsy. These are divided into first-, second-, and third-generation AEDs. The commonly used first-generation AEDs are phenytoin (PHT), phenobarbital (PB), carbamazepine (CBZ), valproic acid (VPA), zonisamide (ZNS), and clobazam (CLB). The third-generation drug includes lacosamide

(LCM) and eslicarbazepine acetate; others recently delivered are included in the second generation. Post-second-generation AEDs were commonly known as new AEDs. Gabapentin (GBP), topiramate (TPM), lamotrigine (LTG), levetiracetam (LEV), and rufinamide (RFN) are distributed as oral drugs [4].

Diagnosing epilepsy after a single unprovoked seizure when there was high risk for recurrence may or may not lead to a decision to initiate treatment. The proposed practical definition may provide support to a physician who wants to treat a patient with high recurrence risk after a single unprovoked seizure. However, a treatment decision was distinct from a diagnosis, and should be individualized depending upon the desires of the patient, the individual risk-benefit ratio and the available options. The physician should weigh the possible avoidance of a second seizure with associated risks against the risk for drug-related side effects and costs for the patients. To be clear, the diagnosis of epilepsy and a decision to treat were two related but different issues. Many neurologists treat for a time after an acute symptomatic seizure (for example, with Herpes encephalitis), with no implication of epilepsy. In contrast, patients with mild seizures, with seizures at very long intervals, or those declining therapy might go untreated even when a diagnosis of epilepsy is beyond dispute. Clinicians will have to individualize a determination of whether epilepsy is resolved. While a majority of patients with epilepsy are able to maintain seizure control with one to two antiepileptic drugs (AEDs), many individuals require adjunctive therapy to achieve long-term remission. Hence the implications of seizure differ according to the clinicians' awareness about the patient's condition, knowledge about drugs and perspective about epilepsy treatment modalities [5,6]. Despite the availability of new anti-epileptic drugs during the past three decades, repeated outcome analyses showed that > 30% fail to achieve prolonged seizure freedom with medical treatment.

New treatment methods were needed to improve seizure control while not affecting the patient's quality of life by adverse effects. Brivaracetam (BRV), an analog of levetiracetam (LEV), was discovered during a target-based rational drug discovery program. Although preclinical and post-marketing studies suggested broad spectrum of efficacy, BRV is currently only approved as monotherapy and adjunctive therapy of focal-onset seizures in patients age 4 years and older. Studies suggested that behavioral adverse events were likely to be less frequent and less severe with BRV than LEV. Therefore, switching to BRV may be considered for patients who have seizure control with levetiracetam (LEV), but who cannot tolerate its behavioral adverse effects [7]. BRV treatment could improve psychobehavioral adverse events such as aggression and depressive symptoms associated with previous LEV treatment. However, because of a small number of patients and descriptive nature of the results, the quality of evidence was low [8]. Understanding the prevalence, treatment options, and prescription behavior in the context of epilepsy is crucial for improved patient management and enhanced quality of life. This study explores the current landscape of epilepsy in India, focusing on pharmacotherapy, epidemiology, and the latest developments in treatment, with a comparative analysis of two commonly used antiepileptic drugs such as brivaracetam and levetiracetam.

## Methods

We carried out a cross sectional, multiple-response questionnaire based survey among clinicians specialized in treating epilepsy patients in the major Indian cities from June 2022 to December 2022.

## Questionnaire

The questionnaire booklet titled brivaracetam in epilepsy management was sent to the physicians who were interested to participate. The study questionnaire included 20 items about current recommendations, clinical observations, and clinical experience of specialists in the management of epilepsy. The study was conducted after receiving approval from Bangalore Ethics, an Independent Ethics Committee which is recognized by the Indian Regulatory Authority, Drug Controller General of India.

## Participants

Convenience sampling method was adopted where an invitation was sent to leading clinicians who were expertise in managing epilepsy in the month of March 2022 for participation in this Indian survey. About 84 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Those physicians were included and asked to complete the questionnaire without discussing with peers. A written informed consent was obtained from each neurologist's prior initiation of the study. Clinicians who were expertise in other specialities and were not provided informed consent were excluded from the study.

## Statistical analysis

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to depict their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. To visualize the distribution of the categorical variables, pie, and bar charts were created using Microsoft Excel 2013 (version 16.0.13901.20400).

## Results

About 84 questionnaire booklets were distributed to clinicians, in that 82 physicians completed questionnaires and were collected personally by the study coordinators through the duration of 4 weeks. The study indicated that the prevalence of epilepsy was mostly in the range of 21-30 patients in a month as responded by 39% of target doctors. Also, another 33% of respondents treat 11-20 patients in an average month. Only 21% of doctors reported that they consult a maximum of epilepsy of 31-40 cases per month. Less than 10 cases were seen by 6% of the doctors. The study also reported that 65% of respondents observed that epilepsy cases are most common in both Rural and Urban. Incidentally, Rural population solely has more cases 21% of epilepsy than urban with 13%.

Generalized tonic-clonic seizure (48%) and partial onset seizure (48%) were the most common forms of epilepsy presented by the patients during clinical practice. Myoclonic seizure was the least form of epilepsy observed (5%). The study suggested that 49% of doctors require an add on drug to 5-10 patients per month while 41% of patients need add on drug therapy for 10-15 patients in a month. Only

9% of doctors said that they need add on drug for epilepsy for less than 5 patients. It was observed that 49% of doctors treat mostly 11-20 patients with partial onset seizure in their clinical practice, followed by 21% of respondents treat 21-30% of the patients who require an add on drug for epilepsy. Another 22% of doctors see 6-10% of patients who need an add on drug for epilepsy and 9% of doctors see only less than 5% of epilepsy patients. Further, 56% of doctors consider brivaracetam as the most preferred drug for newly diagnosed epilepsy followed by levetiracetam by 27% of respondents, sodium valproate by 10% and carbamazepine by 7% of the respondents [Figure 1].

The prescribing pattern of the study reported mostly, 38% of doctors prescribe levetiracetam for 31-40% of partial onset seizure patients which was the highest percentage prevalence. Another 33% of doctors prescribed levetiracetam for 21-30% of the partial onset seizure patients. On the other hand, only 15% of doctors prescribe less than 40% and greater than 40% of partial onset seizure patients are on Levetiracetam each. Also, the study observed that 39% doctors conveying 21-30% of their patients treated with levetiracetam remain uncontrolled. Another 35% of doctors observed that less than 10% of their patients treated with levetiracetam remain uncontrolled. The lowest incidences were reported by 18% of doctors at 11-20% and 7% of doctors at 31-40% of their patients treated with levetiracetam remain uncontrolled.

Both behavioural and psychiatric adverse effects were the most common reason for discontinuation of levetiracetam as suggested by 55% of the respondents. Another 27% doctors attributed behavioural adverse effects and 18% considered psychiatric adverse effects as the reason discontinuation of levetiracetam. The study also reported that 73% of doctors prescribe brivaracetam for the patients failed on levetiracetam which was the maximum choice of the target doctors. Oxcarbazepine of 12% and valproic acid of 10% were the immediate choices of preference if Levetiracetam fails. Additionally, 40% of doctors reported their patients experiencing behavioural changes with levetiracetam to 10-20% of their patients while 30% with less than 10% of patients experiencing behavioral changes and 29% have experienced with 20-30% of patients having behavioural changes with levetiracetam.

When the study analyzed the response of doctors regarding the percentage of patients experiencing behavioral changes with levetiracetam shifted to brivaracetam, the study reported 38% of doctors conveying behavioural changes with levetiracetam to 10-20% of their patients while 23% have experienced with less than 10% of patients and 29% have experienced with 20-30% of patients

with behavioural changes with levetiracetam shifted to brivaracetam. The study also revealed that 44% of doctors reported that 20-30% of patients in their practice after shifted to brivaracetam from levetiracetam has shown improvement in efficacy and behavioural changes. Another 38% of doctors said 10-20% of patients in their practice after shifted to brivaracetam from levetiracetam presented improvement in efficacy and behavioural changes. The least number of doctors reported that 15% of patients in their practice after shifting to brivaracetam from levetiracetam had improvement in efficacy and behavioural changes.

About 39% of doctors observed 30-50 patients with partial onset seizure on brivaracetam in their clinical practice and another 38% of doctors observed that less than 30 patients were with partial onset seizure patients on brivaracetam in their clinical practice. Another 38% of doctors observed that less than 30 patients were with partial onset seizure patients on brivaracetam in their clinical practice. Nearly 77% of doctors confirmed that there were partial onset seizure patients of brivaracetam on monotherapy in their clinical practice. Only 23% of doctors responded contrarily on the same. About 39% of doctors presented that they have put on the drug with 30-50 patients as monotherapy and another 38% of doctors conveyed monotherapy with less than 30.

The study indicated that 47% of doctors opined that 18-45 years as the most common age group whom brivaracetam is being prescribed. The next most observed age group was 45-60 years as recalled by 23% of respondents [Figure 2]. Almost two third doctors prescribe brivaracetam 100 mg/day in their clinical practice, only 17% of doctors recommended 50 mg/day and 10% of doctors prescribed 75 mg/day.

Almost two third doctors prescribe brivaracetam because of its minimal psychiatric and behavioural adverse effects. Another 17% of doctors prescribe brivaracetam due to its better tolerability and 12% due to its better efficacy. Sustained long term effect was the least mentioned by the doctors by 5% of doctors [Figure 3]. As per

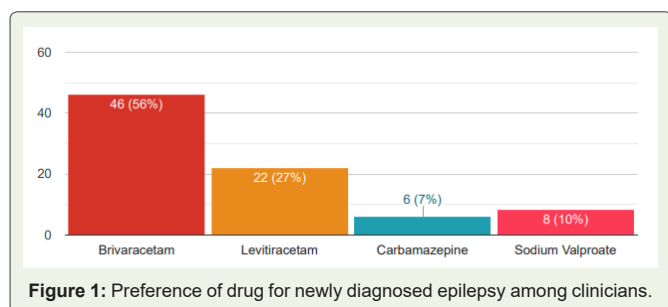


Figure 1: Preference of drug for newly diagnosed epilepsy among clinicians.

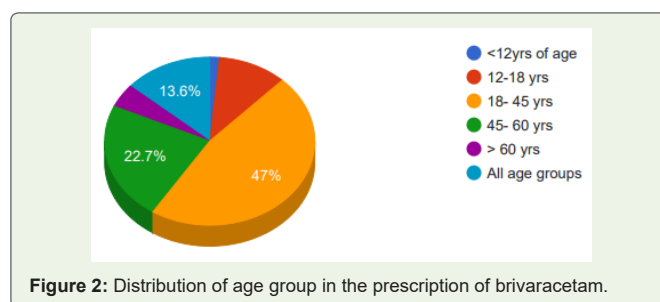


Figure 2: Distribution of age group in the prescription of brivaracetam.

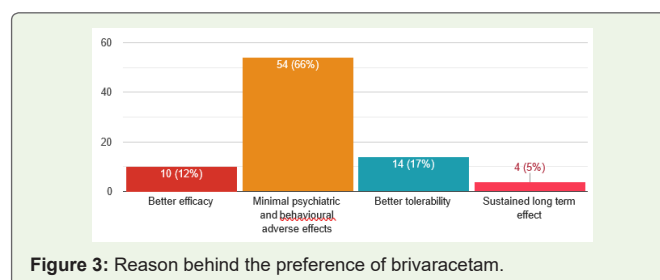


Figure 3: Reason behind the preference of brivaracetam.

the study report, 34% of doctors opined that 21-30 individuals were seizure free with brivaracetam as compared to levetiracetam whereas 30% of doctors consider 31-40 individuals were seizure free with brivaracetam as compared to levetiracetam. Another 18% of doctors consider less than 20 individuals were seizure-free with brivaracetam as compared to levetiracetam in their clinical practice while only 16% of doctors observed that more than 40 individuals were seizure-free with brivaracetam as compared to Levetiracetam in their clinical practice.

## Discussion

The study indicated that a significant number of doctors in India were managing epilepsy cases in their clinical practice. The high number of cases highlighted the substantial burden of epilepsy in the country, necessitating effective treatment strategies. The overall prevalence (3.0-11.9 per 1,000 population) and incidence (0.2-0.6 per 1,000 populations per year) data from recent studies in India on general population were comparable to the rates of high-income countries (HICs) despite marked variations in population characteristics and study methodologies. There was a differential distribution of epilepsy among various sociodemographic and economic groups with higher rates reported for the male gender, rural population, and low socioeconomic status. A changing pattern in the age-specific occurrence of epilepsy with preponderance towards the older age group is noticed due to sociodemographic and epidemiological transition [9].

The study revealed that epilepsy was prevalent in both urban and rural areas. However, it's noteworthy that rural areas have a slightly higher prevalence. This could be attributed to various factors such as limited access to healthcare, lower awareness, and different environmental influences. Based on the total projected population of India in the year 2001, the estimated number of people with epilepsy would be 5.5 million. Based on a single study on the incidence of epilepsy, the number of new cases of epilepsy each year would be close to half a million. Because rural population constitutes 74% of the Indian population, the number of people with epilepsy in rural areas will be approximately 4.1 million, three fourths of whom will not be getting any specific treatment as per the present standard [10].

Generalized tonic-clonic seizures and partial-onset seizures were the most commonly encountered forms of epilepsy in clinical practice. Approximately 20-25% of cases were classified as generalized seizures [11]. The findings of our study as reported from the physicians align with global trends in epilepsy presentation.

The study suggested that a significant proportion of patients require add-on drugs for epilepsy management. This highlighted the challenges in achieving seizure control with monotherapy and emphasized the importance of optimizing treatment regimens. On a survival curve analysis, a comparative study done by Pipek et al., combination therapy was observed to be superior to levetiracetam and lamotrigine monotherapies, and non-inferior to valproic acid monotherapy. Patients without adequate seizure control with these medications in monotherapy, benefited from combination therapy. Combination therapy appears to retain efficacy for longer periods, as suggested by Pipek et al. [12].

Levetiracetam remains a commonly prescribed drug for partial-onset seizures, and a substantial percentage of patients are on this medication. However, it's crucial to address the uncontrolled cases and side effects associated with its use. With a unique mode of action, levetiracetam has opened the door to a new and convincing treatment option for epilepsy. Due to its favorable profile concerning ease of use, almost complete lack of interactions, and excellent efficacy and tolerability it has been globally established as one of the leading AEDs. The development of BRV, its derivative, was completed some years later. Compared with Levetiracetam, brivaracetam, that acts more selectively at the synaptic vesicle protein 2A (SV2A) binding site, offers typically better tolerability in relation to psychiatric adverse events [13-15]. The authors and other studies found that in patients with these adverse events, an immediate switch from Levetiracetam to brivaracetam was easily achieved with a practical routine [16].

Behavioral and psychiatric adverse effects were identified as the primary reasons for discontinuing levetiracetam. This underscores the importance of monitoring and managing side effects in epilepsy patients. Our study observed 38% of doctors conveying the prevalence of behavioral abnormalities among patients. The results were similar to Oluwaseun Ogunsakin et al. where they concluded as though, the drug has a convenient dosing regimen and was relatively well tolerated, neuropsychiatric side effects can emerge beyond the initial titration period and may be the most common reason for drug discontinuation. Levetiracetam has been reported to cause varying degrees of psychiatric adverse effects including behavioral disturbance such as agitation, hostility and psychosis, and mood symptoms and suicidality [17].

A significant proportion of doctors opted for brivaracetam when patients failed to respond to levetiracetam. This transition suggested confidence in brivaracetam's potential to improve seizure control and minimize adverse effects. As suggested by L. Abaira et al., the safety and tolerability, an overnight switching to brivaracetam was safe and well tolerated. This treatment can improve levetiracetam-related neuropsychiatric AEs [18]. The study reported that many patients experience improvement in both efficacy and behavioral changes after shifting to brivaracetam. This outcome supported the clinical utility of brivaracetam in challenging cases.

A substantial number of doctors prescribe brivaracetam as monotherapy for partial-onset seizures. This approach aligns with the goal of simplifying treatment regimens and enhancing patient compliance. Doctors perceive brivaracetam advantages to include minimal psychiatric and behavioral adverse effects, better tolerability, and improved efficacy. These factors contribute to its popularity among physicians. A notable percentage of doctors believe that more individuals achieved seizure freedom with brivaracetam compared to levetiracetam. This finding underscored brivaracetam potential to offer improved outcomes for epilepsy patients [19,21].

Despite these advancements, challenges such as uncontrolled seizures and medication-related side effects persist. Therefore, ongoing research and clinical monitoring are crucial to further enhance epilepsy management in India and improve the quality of life for individuals living with this condition.



## Conclusion

The study's findings shed light on the current landscape of epilepsy management in India. With a significant number of cases being managed by healthcare professionals, there was an emerging need for effective treatment options that can address the diverse needs and challenges presented by epilepsy patients. Brivaracetam has emerged as a preferred choice, especially for newly diagnosed patients and those who do not respond adequately to levetiracetam. Its perceived advantages, including minimal adverse effects and improved efficacy, make it a valuable addition to the arsenal of antiepileptic drugs. Lack of sufficient response to anti-epileptic drugs are common in seizure patients. Combination therapy has gained attention as add-on medications presented pronounced prognosis in epilepsy management. The intervention of brivaracetam had been observed with minimum adverse effects, better tolerability and enhanced efficacy. An overnight switching to the drug produced effective management and finer seizure control in patients. Response from clinicians comply very well with trial reports. Further trials and studies on interactions and adverse effects of the drug are highly recommended.

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