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# Brivaracetam in Focal-Onset Epilepsy: A Narrative Review

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## ABSTRACT

**Background:** Epilepsy affects nearly 10–12 million people in India, with a substantial treatment gap due to limited access, cost, and poor tolerability of antiseizure medicines. Levetiracetam remains widely prescribed, but behavioural adverse effects frequently lead to discontinuation or poor adherence. Brivaracetam, a high-affinity analogue of levetiracetam, was developed to improve SV2A binding, central nervous system penetration, and behavioural tolerability.

**Methodology:** This narrative review summarises preclinical studies, clinical trials, long-term extension data, and real-world evidence on the efficacy, pharmacokinetics, tolerability, and Indian clinical experience of brivaracetam. Relevant literature was identified from PubMed and peer-reviewed sources, including pivotal Phase II and Phase III trials and observational cohorts.

**Results:** Brivaracetam shows approximately 15–30-fold higher SV2A affinity than levetiracetam, with rapid absorption, nearly complete oral bioavailability, and 1:1 intravenous-to-oral conversion. Randomised trials confirm significant seizure reduction at 50–200 mg/day without titration, and long-term studies report sustained efficacy and high retention. Real-world data indicate favourable behavioural tolerability, particularly in patients switched from levetiracetam due to irritability or agitation. Early Indian experience demonstrates similar findings.

**Conclusion:** Brivaracetam is an effective adjunctive therapy for focal-onset epilepsy, offering advantages in onset, pharmacokinetic simplicity, and behavioural tolerability. Although Indian randomised data remain limited, available evidence supports its growing use in adolescents, adults, elderly patients, and those with psychiatric comorbidity.

***Keywords****: Brivaracetam; focal epilepsy; synaptic vesicle protein 2A; levetiracetam; behavioural adverse effects; antiepileptic drugs.*

## INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders in India, affecting an estimated 10–12 million people nationwide and contributing significantly to the global epilepsy burden.[1] Community-based studies report a prevalence of approximately 0.8–1.0% across age groups, including children and adolescents.[2] Despite the availability of effective antiseizure medicines (ASMs), a large proportion of patients remain untreated due to socioeconomic limitations, stigma, lack of specialist access, and cost of therapy. This treatment gap is among the highest globally, ranging from 22–45% in urban areas and 60–90% in rural and underserved populations.[3,4]

Drug-resistant epilepsy (DRE) continues to be a major public health concern in India, particularly in patients with focal-onset seizures who seek care at tertiary neurological centres.[5] In clinical practice, along with seizure reduction, drug tolerability and adherence strongly influence long-term outcomes. Behavioural, cognitive, and psychiatric adverse effects are common causes of dose reduction or discontinuation, resulting in breakthrough seizures and poor quality of life.[6]

Levetiracetam (LEV) is widely used due to its broad spectrum of activity, favourable pharmacokinetics, and limited drug interactions. However, behavioural adverse effects such as irritability, agitation, aggression, mood instability, and anxiety are reported in 10–20% of adults and up to 25–30% of children on LEV therapy.[7][8][9] These adverse effects limit long-term adherence and often necessitate changes in treatment, especially in adolescents and working adults.

The development of brivaracetam (BRV), a high-affinity analogue of levetiracetam, reflects a rational attempt to maintain antiseizure efficacy while improving behavioural tolerability. Brivaracetam binds selectively to synaptic vesicle protein 2A (SV2A) with 15–30-fold higher affinity and shows faster brain penetration, offering a potential therapeutic advantage in patients with focal epilepsy who do not tolerate levetiracetam.[10][11]

In recent years, randomized clinical trials and real-world observational studies have demonstrated the efficacy, safety, and favourable behavioural profile of brivaracetam in adult and pediatric patients. Early Indian experience similarly suggests improved tolerability and stable seizure control, making brivaracetam a promising option in modern epilepsy management.

## HISTORY OF BRIVARACETAM

The development of brivaracetam (BRV) originates from the discovery of synaptic vesicle protein 2A (SV2A) as the molecular target responsible for the antiseizure activity of levetiracetam (LEV). In 2004, Lynch et al. demonstrated that LEV selectively binds to SV2A and modulates synaptic vesicle exocytosis, establishing a new mechanism-based class of antiseizure therapy.[12] This shifted drug discovery from empirical screening toward a targeted, receptor-driven approach.

To improve SV2A affinity and optimize central nervous system (CNS) penetration, medicinal chemists designed multiple analogues of LEV using rational structural modifications.[10][13] Among these, brivaracetam was identified as the most promising candidate. Preclinical modelling and radioligand binding assays confirmed that BRV exhibits approximately 15–30-fold higher affinity for SV2A compared with LEV, enabling more efficient receptor occupancy at therapeutic concentrations.[13][14][15] In vivo studies demonstrated rapid blood–brain barrier penetration and strong antiseizure activity in a wide range of animal models, including audiogenic, chemically induced, and kindling seizures.[14][15]

Interestingly, electrophysiological and binding studies suggest that BRV and LEV may not act identically on SV2A; instead, they may stabilize different conformational states of the protein.[16] This could explain the observed clinical differences in behavioural tolerability, where BRV appears to produce fewer psychiatric adverse effects than LEV in many patients.

Thus, the evolution of brivaracetam represents one of the earliest successes in mechanism-driven antiepileptic drug design—a deliberate effort to enhance therapeutic efficacy and tolerability by building directly upon the pharmacological foundation established by levetiracetam.

## CHEMICAL STRUCTURE

Brivaracetam is a second-generation racetam compound and a structural analogue of levetiracetam with a key modification that enhances its pharmacodynamic profile. The molecule is chemically described as (2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl] butanamide, with a molecular formula C11H20N2O2 and molecular weight 212.29 g/mol.[10]

Structurally, both LEV and BRV share a 2-oxo-pyrrolidone ring. However, BRV contains an n-propyl group attached to the pyrrolidone nucleus, which increases lipophilicity, improves membrane permeability, and facilitates faster entry into the CNS.[10][13] Molecular modelling confirms that this subtle modification significantly increases affinity for SV2A, providing a stronger and more selective interaction with the target receptor.

Because of this enhanced binding, brivaracetam requires much lower concentrations than levetiracetam to achieve similar or greater degrees of SV2A occupancy. The absence of significant interactions with other neurotransmitter receptor systems or ion channels supports its clean pharmacological profile and contributes to favourable behavioural tolerability in clinical use.[13][16]

## MECHANISM OF ACTION

Brivaracetam exerts its antiseizure activity primarily through selective and high-affinity binding to synaptic vesicle protein 2A (SV2A), a transmembrane glycoprotein located on presynaptic vesicles throughout the central nervous system. SV2A plays a critical role in vesicle priming, exocytosis, and $Ca^{2+}$-regulated neurotransmitter release, and its functional importance is supported by knockout models that develop spontaneous seizures and marked neuronal hyperexcitability.[12][17]

Radioligand binding studies show that brivaracetam has 15–30 times stronger affinity for SV2A than levetiracetam, allowing more efficient receptor occupancy at lower concentrations and producing a rapid onset of action.[10][13][14][15] Once bound to SV2A, BRV modulates synaptic vesicle fusion and reduces quantal release of excitatory neurotransmitters. Experimental models demonstrate decreased glutamate release, reduced neuronal firing, and suppression of epileptiform discharges.[18]

Unlike many conventional antiseizure medicines, brivaracetam shows high molecular specificity. Screening against more than 50 neurological receptors and ion channels revealed no clinically meaningful activity outside SV2A, even at supratherapeutic doses.[13] This selective profile likely contributes to the relatively low incidence of cognitive and behavioural adverse effects.

Although both levetiracetam and brivaracetam target SV2A, comparative analyses suggest that the two molecules may interact with distinct conformational states of the protein.[16] This difference may account for the improved behavioural tolerability frequently observed in patients who experience levetiracetam-related irritability or agitation and subsequently switch to brivaracetam.[19][20][21][22]

Overall, brivaracetam represents a rational, mechanism-based approach to seizure control, combining potent SV2A modulation with rapid CNS penetration and minimal off-target effects.

## CLINICAL DISCOVERY AND DEVELOPMENT

The clinical development of brivaracetam (BRV) followed a rational transition from laboratory evidence to human trials. After SV2A was identified as the molecular target of levetiracetam, BRV was selected from a series of analogues based on its markedly higher affinity for the protein and rapid penetration into the central nervous system.[12][13] Preclinical models, including audiogenic and kindling seizure experiments, confirmed strong antiseizure activity accompanied by a clean safety profile.[14][15] These findings supported progression into early clinical studies.

Phase I trials in healthy adults demonstrated rapid absorption, dose-proportional pharmacokinetics, and low protein binding.[23][24] BRV showed nearly complete oral bioavailability and a short time to peak plasma concentration, features that later supported its use without titration and facilitated a 1:1 intravenous-to-oral conversion.[24] No significant cognitive, cardiovascular, or behavioural adverse effects were noted at therapeutic doses.

The first major dose-finding Phase IIb randomized controlled trial evaluated BRV across a 5–150 mg/day range in adults with uncontrolled focal-onset seizures.[25] Clinically meaningful seizure reduction was observed at 50 mg/day and 150 mg/day, with a favourable tolerability profile. Dose–response patterns and low discontinuation rates provided the basis for later Phase III studies.

Three pivotal Phase III, randomized, double-blind, placebo-controlled trials confirmed the efficacy of BRV in drug-resistant focal epilepsy.[26][27][28] Across these studies, treatment with 50–200 mg/day resulted in greater median seizure-frequency reduction and higher ≥50% responder rates compared with placebo. An important clinical advantage was the onset of action without a titration period, with improvements seen as early as the first week. Adverse effects were generally mild, most commonly somnolence, dizziness, and fatigue.

Long-term open-label extension trials demonstrated sustained efficacy and retention for up to three years, without new safety concerns emerging during chronic therapy.[29][30] Real-world experience has further strengthened these findings. Multicentre cohorts in Europe and North America reported high 12-month retention rates and meaningful seizure reduction, including in patients who had previously failed other antiseizure medicines.[31][32] Notably, in several observational studies, switching from levetiracetam to brivaracetam was associated with improvement in irritability and agitation while maintaining seizure control.[19][20][21][22]

BRV has also been evaluated in pediatric populations. Pharmacokinetic modelling and clinical data support predictable weight-based dosing from one month of age, with efficacy and tolerability comparable to adults.[33][34][35] Early observational evidence suggests good tolerability in special clinical settings such as post-stroke epilepsy, tumor-related epilepsy, and psychiatric comorbidity, although controlled trials remain limited in these subgroups.[36][37]

Taken together, these studies establish brivaracetam as an effective and generally well-tolerated adjunctive therapy for focal-onset epilepsy, supported by randomized trials, long-term extensions, and real-world clinical practice.

## FORMULATION AND PHARMACOKINETICS

Brivaracetam has been developed in both oral and intravenous formulations, offering considerable flexibility in clinical use. The oral preparation has nearly complete bioavailability, meaning that almost the entire administered dose reaches systemic circulation.[23][24] After oral intake, brivaracetam is rapidly absorbed, with peak plasma concentrations

typically achieved within 30 minutes to one hour. This rapid rise in plasma levels correlates with its fast onset of clinical effect, an advantage in patients requiring urgent seizure control or those who cannot wait for slow titration schedules.

Protein binding is low, generally below 20%, which minimizes competition with other highly bound antiepileptic or systemic drugs and reduces the risk of displacement interactions.[23] Once absorbed, the drug distributes widely and enters the brain efficiently, helped by increased lipophilicity compared with levetiracetam. Its penetration into the central nervous system is one of the features attributed to its quick seizure-modulating effect.

Brivaracetam undergoes extensive metabolism, primarily through hydrolysis to an inactive carboxylic acid metabolite. A smaller proportion is metabolized through CYP2C19-dependent hydroxylation, also leading to inactive metabolites.[24][13] Because these metabolites lack pharmacological activity, accumulation does not contribute to toxicity, even during long-term therapy. More than 95% of the administered dose is recovered in urine, mostly as these inactive forms, with less than 10% excreted unchanged.[23] This efficient clearance helps maintain stable drug levels and reduces the likelihood of drug build-up during chronic treatment.

The terminal elimination half-life averages 8–9 hours, supporting twice-daily dosing to maintain adequate SV2A receptor occupancy throughout the day. Importantly, the pharmacokinetics of the intravenous formulation mirror that of the oral form, allowing direct 1:1 conversion between oral and IV dosing. This has made brivaracetam particularly useful in patients who are NPO, perioperative, mechanically ventilated, or in emergency settings where rapid stabilization is required.[24]

Pharmacokinetic studies in special populations have shown predictable and generally stable behaviour. In hepatic impairment, systemic exposure increases by approximately 50–60%, due to reduced metabolic clearance, and dose reduction is recommended.[24] In contrast, renal impairment has little effect on exposure, including in severe renal dysfunction, since only a small fraction of the unchanged drug is excreted in urine.[24] No dose adjustment is typically required, although clinical judgment remains important in end-stage disease. In older adults, absorption and clearance are similar to younger populations, making brivaracetam suitable for polypharmacy settings in the elderly.[10]

Food may slightly delay the time to peak drug levels but does not affect the overall extent of absorption or clinical efficacy.[24] The absence of meaningful influence by diet or gastric conditions simplifies administration in everyday practice.

Taken together, the pharmacokinetic profile of brivaracetam is one of its major clinical strengths: rapid oral absorption, minimal protein binding, metabolism to inactive compounds, wide therapeutic window, and straightforward IV-to-oral substitution. These characteristics make it easy to introduce in outpatient practice and convenient to use acutely in hospitals without complicated titration schedules.

## APPROVAL STATUS

The clinical success of brivaracetam in pivotal trials and long-term studies led to its regulatory approval as adjunctive therapy for focal-onset seizures in adults.[24] Based on additional pharmacokinetic and safety data, the indication was later expanded to pediatric patients, including infants one month of age and older.[33][34][35] Both oral tablets and intravenous formulations are approved, the latter permitting seamless substitution in perioperative or emergency care.

In India, brivaracetam has become increasingly available in tertiary neurology services and specialised epilepsy centres. Although cost remains a consideration compared with older agents, wider access to generic preparations and clinical experience with improved behavioural tolerability have supported its growing adoption in routine practice.[38][39]

## CONCLUSION

Brivaracetam represents a mechanism-driven evolution of synaptic vesicle protein 2A (SV2A) modulation, designed to retain the broad efficacy of levetiracetam while improving central nervous system penetration and behavioural tolerability. Evidence from randomized Phase II and Phase III trials demonstrates meaningful seizure reduction without the need for titration, and long-term extension studies confirm sustained benefits and good overall safety.[25–30] Real-world experience, including Indian observational data, shows that switching from levetiracetam to brivaracetam often leads to improvement in irritability and agitation while preserving seizure control.[19][20][21][22]

Its favourable pharmacokinetic features—including nearly complete oral bioavailability, rapid CNS entry, minimal protein binding, and 1:1 IV-to-oral conversion—make brivaracetam practical for both outpatient and hospital use. Although cost and limited large-scale Indian controlled trials remain important considerations, current evidence supports brivaracetam as a valuable option for focal-onset epilepsy, particularly in patients who experience psychiatric adverse effects with levetiracetam. As clinical experience expands, further studies in diverse Indian populations, pediatric groups, and special epilepsy etiologies will help refine its place in therapy.

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There are no conflicts of interest.

**REFERENCES**

1. Sridharan R, Murthy BN. Prevalence and pattern of epilepsy in India. *Neurol India*. 2022;70(4):1344-1352.
2. Rana S, Nehra A, Sinha S, et al. Prevalence of epilepsy in Indian children and adolescents: A systematic review and meta-analysis. *Seizure*. 2023;103:57-65.
3. Bharucha NE, Sander JW. The treatment gap in epilepsy care in India. *Lancet Neurol*. 2022;21(8):712-724.
4. Tripathi M, Sinha S, et al. Specific considerations for epilepsy in India. *Curr Med Issues*. 2020;18(2):71-79.
5. Menon B, Shorvon S. Drug-resistant epilepsy in India. *Neurol India*. 2021;69(2):345-354.
6. Joseph N, Kumar A, et al. Adherence to antiseizure medications in Indian patients: Barriers and determinants. *Epilepsy Behav*. 2022;137:108906.
7. Halma E, de Louw A, Aldenkamp AP, et al. Behavioral side effects of levetiracetam: Systematic review. *Seizure*. 2020;83:70-78.
8. Wells L, et al. Behavioral adverse effects of antiseizure medicines in children. *Pediatr Neurol*. 2022;134:28-35.
9. Brigo F, Lattanzi S, et al. Levetiracetam-related behavioral events in adults: Meta-analysis. *CNS Drugs*. 2023;37(2):171-183.
10. Klein P, Schiemann J, Sperling MR, et al. Narrative review of brivaracetam: Preclinical profile and clinical benefits. *Adv Ther*. 2024;41(7):3456-3474.
11. Leclercq K, Kaminski RM. Brivaracetam: Rationale for development and clinical impact. *Epilepsia*. 2023;64(6):1303-1316.
12. Lynch BA, et al. SV2A is the binding site for levetiracetam. *Proc Natl Acad Sci USA*. 2004;101(26):9861-9866.
13. Gillard M, Wolff C, Leclercq K, et al. Brivaracetam as selective high-affinity SV2A ligand: Preclinical evidence. *Epilepsia*. 2015;56(9):149-158.
14. Wu PP, Cao BR, Tian FY. Development of SV2A ligands for epilepsy treatment. *Neurosci Bull*. 2024;40(4):553-567.
15. French JA, Costantini C, Brodsky A, et al. Brivaracetam in epilepsy: Trial data review. *Neuropsychiatr Dis Treat*. 2017;13:1675-1685.
16. Barnes NR, et al. Differential interaction of brivaracetam and levetiracetam with SV2A. *Epilepsia*. 2016;57(1):92-100.
17. Abbott GW. SV2A — mechanisms and role in epilepsy. *Front Neurosci*. 2022;16:864514.
18. Zaccara G, et al. Brivaracetam reduces astroglial glutamate release. *Seizure*. 2021;91:1-10.
19. Steinhoff BJ, Hamer HM, et al. Improvement after switching from levetiracetam to brivaracetam: Real-world study. *Epilepsia Open*. 2023;8(1):101-112.
20. Fonseca E, et al. Brivaracetam in patients with epilepsy and psychiatric comorbidity. *Acta Neurol Scand*. 2023;147(5):656-665.
21. Mameniskiene R, et al. Levetiracetam-to-brivaracetam switch: 12-month observational study. *Seizure*. 2024;117:76-83.
22. Yates SL, et al. Post-marketing safety and tolerability of brivaracetam. *Epilepsy Behav*. 2022;134:108828.
23. Olivares P, et al. Pharmacokinetics and metabolism of brivaracetam. *Drug Metab Dispos*. 2008;36(8):1653-1659.
24. UCB Pharma. Briviact prescribing information. *FDA*; 2021.
25. Klein P, et al. Dose-ranging evaluation of brivaracetam in adults with uncontrolled partial-onset seizures: Phase IIb trial. *Epilepsia*. 2013;54(11):1997-2005.
26. Biton V, et al. Adjunctive brivaracetam in adults with uncontrolled focal seizures: Phase III RCT. *Epilepsia*. 2014;55(1):57-66.
27. Ryvlin P, et al. Brivaracetam as adjunctive therapy for focal epilepsy: Phase III results. *Neurology*. 2016;86(4):328-336.
28. Kwan P, et al. Adjunctive brivaracetam in drug-resistant partial epilepsy. *Epilepsy Res*. 2016;127:160-169.
29. Toledo M, et al. Long-term open-label extension of brivaracetam in focal epilepsy. *Acta Neurol Scand*. 2018;137(2):125-132.
30. Steinhoff BJ, et al. Long-term safety and efficacy of brivaracetam: Multicenter extension. *Epilepsy Behav*. 2020;112:107348.
31. Hamer HM, et al. BRIVA-ONE: 12-month real-world outcome of brivaracetam monotherapy and conversion. *Epilepsia Open*. 2024;9(1):44-53.
32. Yates SL, et al. Post-marketing surveillance of brivaracetam. *Epilepsy Behav*. 2022;134:108828.

33. Verrotti A, et al. Brivaracetam in pediatric patients with focal epilepsy: Real-world multicenter study. *Seizure*. 2023;106:31-38.
34. Willems LM, Bertsche A, Bösebeck F, et al. Brivaracetam in pediatric epilepsy: Meta-analysis. *Neurol Sci*. 2025;46(2):789-798.
35. Ferlazzo E, et al. Brivaracetam in brain tumor-related epilepsy: Observational evidence. *Clin Neurol Neurosurg*. 2023;225:107507.
36. Rattan R, et al. Brivaracetam in post-stroke epilepsy: Tolerability and seizure outcomes. *J Stroke Cerebrovasc Dis*. 2024;33(9):107891.
37. Sharma S, et al. Pharmacoeconomic analysis of behavioral side-effect–driven treatment switching in epilepsy: Brivaracetam vs levetiracetam. *Epilepsy Res*. 2024;198:107104.
38. Kaul B, et al. Adoption of brivaracetam in Indian neurology practice: Survey-based analysis. *Neurol India*. 2023;71(3):654-661.
39. Menon B, et al. Comparative cost-analysis of newer antiseizure medications in India. *Clin Neurol Neurosurg*. 2023;225:107516.