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Review Article

Brivaracetam: A Superior Alternative in Antiepileptic Drug Therapy

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ABSTRACT

Epilepsy affects approximately 70 million people worldwide, with nearly one-third experiencing drug-resistant seizures. Brivaracetam (BRV), a novel antiepileptic drug, exhibits enhanced brain permeability and higher binding affinity to synaptic vesicle protein 2A (SV2A), offering potential therapeutic advantages. This review summarizes data from clinical trials, meta-analyses, and real-world studies from various databases like PubMed, Cochrane etc. on the pharmacokinetics, efficacy, safety, and tolerability of BRV. Comparative evaluation with Levetiracetam (LEV) and application in special populations were also assessed. BRV demonstrated significant seizure reduction, including up to 76.2% reduction in focal-to-bilateral tonic-clonic seizures. It was associated with fewer behavioral adverse effects compared to LEV, including reduced aggression and fatigue. Favorable outcomes were observed in pediatric, geriatric, and drug-resistant populations, including status epilepticus cases. BRV offers a promising alternative in epilepsy treatment, combining rapid brain penetration, robust seizure control, and a superior safety profile. Further studies are warranted in special populations, including pregnant women and children.

INTRODUCTION

Epilepsy is a chronic neurological disorder affecting approximately 70 million people globally, with an annual incidence of 80 per 100,000 and a prevalence of 5–10 per 1,000 individuals [1]. It is characterized by sudden abnormal electrical activity in the brain, leading to seizures, convulsions, or loss of consciousness [2]. Current antiepileptic drugs (AEDs) primarily function by altering brain excitability mechanisms, such as blocking sodium channels (e.g., phenytoin, carbamazepine, lamotrigine) or enhancing GABA transmission (e.g., barbiturates, benzodiazepines) [3,4].

Despite advancements in AEDs, approximately one-third of patients experience uncontrolled seizures, emphasizing the need for novel therapeutic options [5]. Additionally, many AEDs

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are associated with significant behavioral and psychiatric side effects, such as mood instability and aggression, complicating treatment decisions [4].

Brivaracetam (BRV), a next-generation AED approved for epilepsy management, addresses many limitations of traditional drugs. With superior brain permeability, selectivity, and a distinct mechanism of action, BRV offers improved efficacy and tolerability [6]. This review explores the pharmacological, clinical, and economic advantages of Brivaracetam, highlighting its role in enhancing epilepsy care.

BRIVARACETAM-PHARMACOKINETICS AND PHARMACODYNAMICS

Brivaracetam (BRV) exhibits linear pharmacokinetics across a wide dosage range, with nearly complete and rapid absorption following oral administration. The drug has an elimination half-life of approximately eight hours and a low plasma protein binding rate of 20% [7].

BRV's enhanced permeability through the blood-brain barrier (BBB) allows for a faster onset of action compared to Levetiracetam (LEV) [8]. Preclinical studies have demonstrated that BRV achieves peak brain concentrations within minutes, while LEV requires approximately one hour [9,10]. This superior brain penetration has been validated in physiologically based pharmacokinetic models and animal studies using audiogenic mice and rhesus monkeys .

BRV is primarily metabolized via hydrolysis mediated by CYP2C19, with secondary hydroxylation pathways. Its metabolites are pharmacologically inactive, and most of the drug (including 8.6% unchanged) is excreted in urine.

THE EFFECTIVENESS

Brivaracetam (BRV) has demonstrated robust efficacy in reducing seizure frequency across various patient populations. In a study on photosensitive epilepsy, a single BRV dose effectively reduced or eliminated EEG discharges induced by photic stimulation at doses ranging from 10 to 80 mg [11].

A meta-analysis by Chen et al. (2024) ranked BRV highest among third-generation AEDs for achieving seizure freedom, with significant reductions in seizure episodes compared to placebo and other AEDs [12]. In patients with focal-onset seizures, BRV monotherapy achieved up to a 76.2% reduction in focal-to-bilateral tonic-clonic seizure frequency [13].

Long-term post-marketing studies have further validated BRV's effectiveness in drug-resistant epilepsy, with patients reporting sustained seizure control and improved quality of life. BRV's ability to achieve rapid and effective seizure control makes it a valuable addition to epilepsy management [14].

SAFETY:

Brivaracetam (BRV) is distinguished by its favorable safety profile, attributed to its high selectivity and specificity for SV2A receptors [12]. Clinical trials consistently report low incidences of treatment-emergent adverse events (TEAEs) such as headache (10%), dizziness (15%), and somnolence (12%), with rates comparable to placebo [15].

Preclinical studies further support BRV's reduced behavioral toxicity. In an animal model comparing Brivaracetam to Levetiracetam, BRV-treated rats displayed aggression levels similar to control groups, whereas Levetiracetam significantly increased aggressive behavior [16]. This difference

highlights BRV's advantage for patients at risk of psychiatric side effects.

Additionally, discontinuation rates due to fatigue or behavioral disturbances are significantly lower with BRV than with other AEDs. While some reports note mild psychological side effects, such as increased anger scores, these findings did not reach statistical significance and require further investigation in larger populations [17]. .

TOLERABILITY:

Tolerability is a critical factor in the management of epilepsy, particularly for patients experiencing adverse behavioral and psychiatric side effects from AEDs. Brivaracetam (BRV) has demonstrated excellent tolerability in both clinical trials and real-world studies, with significantly lower rates of behavioral complaints compared to Levetiracetam.

Patient-centered studies, such as the BRIVA-LIFE trial, report improvements in emotional well-being and quality of life following a switch from Levetiracetam to BRV [13]. Withdrawal rates due to intolerable side effects were notably lower for BRV than other AEDs. Furthermore, BRV is well-tolerated in populations prone to behavioral comorbidities, such as those with epileptic encephalopathies [3].

These findings underline BRV's role as a preferred AED, especially for patients previously intolerant to other treatments.

RACETAM CLASS- BRIVARACETAM AHEAD:

A comparative summary of Brivaracetam and Levetiracetam is presented in **Table 1**, highlighting the pharmacological, clinical, and safety advantages of BRV.Despite having the same mode of action, LEV and BRV bind to the human synaptic vesicle 2A (SV2A) protein at locations that are roughly linked to one another, but they do so in distinct ways [18]. Preclinical evidence reveals that BRV is more powerful than LEV due to its strong affinity for the SV2A binding site. The selective SV2A binding mechanism of BRV does not involve α-amino-3-OH-5-methyl-4- isoxazolepropionic acid receptor (AMPA) antagonism, a characteristic that differentiates it from LEV [19]. Patients with drug resistant or generalised epilepsy, who don't respond to LEV will be benefited from BRV treatment which proved to be effective in those patients [20]. Monotherapy with BRV appeared safe and was well tolerated with a reduction of LEV-associated AE in the majority of patients [21].

Table 1: Summary Table: BRV vs LEV Comparison

FEATURE	BRIVARACETAM (BRV)	LEVETIRACETAM (LEV)
SV2A Binding Affinity	Higher	Lower
Brain Penetration	Faster (within minutes)	Slower (up to 1 hour)
Common Behavioral Side Effects	Lower (less aggression, irritability)	Higher (aggression, mood changes)
Half-Life	~8 hours	~7 hours
Plasma Protein Binding	~20%	<10%
Psychiatric Tolerability	Superior	Inferior
Pediatric Use	Off-label, under investigation	Approved
Pregnancy Data	Limited, lower teratogenicity risk suspected	More data, moderate teratogenicity risk
Status Epilepticus Use	Emerging evidence supports IV BRV use	Not typically used

Despite structural similarities, LEV has been associated with more psychiatric side effects compared to BRV. [22] However, brivaracetam has been shown to generate fewer negative effects in numerous studies. BRIVA-LIFE study showed that patient had increased tolerance after switching from LEV to BRV. Brivaracetam administration improved emotional well-being and quality of life from baseline. [13] The patients who experienced adverse events due to LEV had a significant decrease in AEs after switching to BRV. Behavioral side effects and psychiatric comorbidities were the primary adverse events that prompted the switch [23]. In some cases, patients were switched back to LEV due to inadequate efficacy with BRV [24] . In contrast to LEV, BRV is unlikely to be linked to aggressive behavior in rodents.

STATUS EPILEPTICUS AND BRIVARACETAM:

Recurrence of seizures even after anticonvulsant medication is the hallmark of status epilepticus, which is divided into several phases based on the kind of treatment the patient is not responding to. When an individual has refractory status epilepticus, they experience seizures at least an hour after beginning anesthesia treatment [25]. In research led by Adam Strzelczyk, individuals with super refractory status epilepticus saw remission within 24 hours after receiving BRV at a dosage of 50–400 mg. Therefore, this study suggests that BRV could be a therapy option for SE [8]. Administration of IV BRV in status epilepticus will respond clinically to treatment within 2 hours and EEG response within 48 hours [21]

SPECIAL POPULATIONS: PEDIATRICS, GERIATRICS, AND PREGNANCY:

Brivaracetam (BRV) shows promising potential across diverse patient populations, including children, the elderly, and pregnant women, though data remains limited in some areas.

PEDIATRICS

While BRV is not yet approved for pediatric use, emerging evidence supports its efficacy and safety in this population. Off-label studies indicate significant reductions in seizure frequency in children with drug-resistant epilepsy [26]. Recommended dosing for pediatric patients includes 2 mg/kg twice daily, with a daily maximum of 200 mg [27]. Children with epileptic encephalopathies or behavioral disturbances transitioning from Levetiracetam have shown marked improvement with BRV [28].

GERIATRICS

BRV has been well-tolerated in elderly patients, with higher seizure control rates and no increase in treatment-emergent adverse effects compared to placebo [29]. Unlike enzyme-inducing AEDs such as carbamazepine or phenytoin, BRV does not exacerbate risks like osteoporosis, vascular complications, or cognitive decline, making it a safer choice for older adults [30].

PREGNANCY

Limited data exists on BRV use during pregnancy, but its lower teratogenic risk compared to traditional AEDs makes it a potential candidate for future research. Studies indicate that BRV lacks the significant teratogenic and cognitive developmental risks associated with Valproate and other older AEDs [31-34].

CONCLUSION:

Brivaracetam (BRV) represents a significant advancement in epilepsy management, combining superior pharmacokinetics with an improved safety and tolerability profile. Its rapid onset of

action, enhanced blood-brain barrier permeability, and selective SV2A receptor binding make it highly effective in reducing seizure frequency, even in drug-resistant cases.

Clinical and preclinical evidence underscores BRV's potential to minimize behavioral and cognitive side effects, setting it apart from traditional AEDs. Additionally, its broad applicability across pediatric, geriatric, and refractory populations enhances its clinical utility.

While current findings establish BRV as a promising alternative, further studies are warranted to explore its long-term efficacy in special populations, such as pregnant women and young children. With its unique properties, BRV holds the potential to significantly improve epilepsy management and patient quality of life. Future randomized controlled trials are warranted to further establish brivaracetam's role, particularly in status epilepticus, pediatric populations, and during pregnancy, where current evidence remains limited.

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