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A SYSTEMATIC REVIEW ON THE CURRENT STATUS OF BRIVARACETAM AS A MONOTHERAPY

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ABSTRACT
Brivaracetam (BRV) is the most recent Anti-Epileptic Drug to be licensed in Europe and the United States as an adjunctive treatment of focal onset seizures with or without secondary generalization. BRV was developed subsequently to develop an anticonvulsant compound with a higher affinity to the binding site synaptic vesicle protein 2A. BRV has been approved as a monotherapy and adjunctive drug in the management of partial-onset (focal) seizures and focal seizures both with and without secondary generalization, in 2018 USFDA has approved BRV as a monotherapy in adults and children above 4 years old, Within the European Union it is only approved as an adjunctive therapy. This review summarizes the essential preclinical and clinical data of BRV that is currently available.

KEYWORDS: Brivaracetam, SV2AEpilepsy, monotherapy.

1. INTRODUCTION

According to the World Health Organization, epilepsy is associated with persistent seizures, which are brief episodes of involuntary movement that can involve a portion of the body (partial) or the entire body (generalized) but are occasionally occurring with loss of consciousness and control of bowel or bladder function. It is the most common chronic neurological condition. Seizure disorders affect nearly 1% of the world's population (50 million),[1] with approximately 80% of patients coming from developing and underdeveloped countries[4], and include focal seizures, generalized epilepsy, and a combination of generalized and focal seizures.[5] These disorders affect approximately 10 million people in India alone.[6] As per World Health Organization (WHO), epileptic seizures are most common in children and young adults in the developing world, while the trend is seen in toddlers and the elderly in developed countries. Despite the availability of new antiepileptic medications, (AEDs) over the previous three decades. Analyses of the outcomes show that more than 30% fail to achieve seizure-free from pharmacotherapy.[3–5] The introduction of novel Anti-epileptic medications is of great importance. Brivaracetam (BRV) is a new prescription medication, it is the most recent AED to be licensed in Europe and the United States as an adjunctive treatment of focal onset seizures with or without secondary generalization.[6-10] BRV was developed subsequently to develop an anticonvulsant compound with a higher affinity to the binding site.[12] Brivaracetam (BRV), a propyl analog of levetiracetam (LEV), is an anticonvulsant with high-affinity binding to synaptic vesicle protein 2A (SV2A). The Food and Drug Administration (FDA) first approved it in 2016 for the adjunctive treatment of focal seizures in patient's adults aged 18 and older. BRV has been approved as a monotherapy and adjunctive drug in the management of partial-onset (focal) seizures in adults and children above 4 years old, since 2018 in the United States. Within the European Union, BRV is only approved as an adjunctive therapy. Treatment of focal seizures both with and without secondary generalization in patients aged 16 and older facing epilepsy. BRV was recently approved in the United States to be used as monotherapy for focal seizures in epileptic patients aged 16 years, with a suggested starting dose of 100 mg/day. BRV at the prescribed dose (50–200 mg/day) for up to 8 years in short-term studies and long-term follow-up research by Toledo.[13] Toledo found that BRV was well tolerated with a rare occurrence of adverse effects. Headache,

lightheadedness, daytime sleepiness, nasopharyngitis, fatigue, and convulsions were the most commonly reported TEAEs (approximately 10 percent).[13]

In patients over the age of 16, focal-onset seizures both with and without secondary generalization are the most common type of epilepsy. Unfortunately, the majority of the first- generation antiepileptic drugs (AEDs)12 was only beneficial in more than half of the patients. The first appropriate drug, levetiracetam, was approved for the treatment of adults in 2000. An overview analysis revealed that, over the last three decades, more than 30% of patients did not achieve freedom from prolonged seizures after treatment with 14 conventional drugs AEDs. Brivaracetam was introduced as an AED in 2004, and it proved to be an unexpected success of rational drug discovery in clinical development, with a 13-fold higher affinity for synaptic vesicle glycoprotein (SV2A) than levetiracetam.

Polytherapy has been used to treat a significant proportion of patients with epilepsy for many years because early monotherapy won't result in all patients being seizure-free. The nature of developing new AEDs, where newer agents are studied 'on top of current therapy to eliminate the unsafe situation of a patient with epilepsy being without effective therapy, maintains the widespread use of polytherapy, and thus newer AEDs are usually approved as adjuvant treatment.[14] This review describes BRV's pharmacological properties, efficacy, tolerability, and safety profiles and overall comprehensive information on brivaracetam as a monotherapy.

2. Brivaracetam Chemical Structure and Discovery

The chemical name of Brivaracetam is BRV ([2S]-2-[(4R) - 2 - oxo - 4 - propyl pyrrolidine-1-yl]butanamide)(C11H20N2O2)5 (BRV) belong to a group of pyrrolidone compounds.[11] It differs from LEV in that a propyl chain was introduced to the lactam ring (figure1), which increased its affinity to the binding site on SV2A.[28] Its molecular formula is C11- H20-N2-O2. It is an n-propyl analog of LEV with a molecular weight of 212.293 g/mol.[11]

BRV, a member of the racetam family of anticonvulsants, was discovered during a target- based rational drug discovery program that was initiated to identify selective, high-affinity SV2A ligands possessing antiepileptic properties superior to LEV. Approximately 12,000 compounds were screened in vitro for SV2A binding affinity. BRV and seletracetam were the two anticonvulsant agents chosen for clinical testing,[12] however, only BRV entered clinical trials, due to its wider spectrum of activity in animal models than seletracetam, and its pronounced ability to inhibit neuronal hyperexcitability.

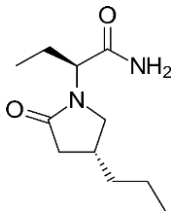

Figure 1: Brivaracetam Structure.

Pharmacokinetics: Rapid absorption of BRV is seen on oral absorption with a maximum absorption time of 1 hour. It has good oral bioavailability; a fatty meal delays the Tmax and decreases Cmax however it doesn't have any effect on bioavailability and takes times to reach peak concentration. Distribution of brivaracetam is only 20% of BRV is bound to proteins and t ½ is 9 hours, it has fast passage to the blood brain barrier. Reaches peak concentrations within minutes after i.v administration. It is metabolized by the liver, primarily by hydrolysis of hepatic amidase and extra-hepatic amidase. Hydroxylation pathway through CYP2C19. Elimination is majorly through the kidney. Pharmacokinetics of brivaracetam is not influenced by age, sex, race and creatinine clearance.

Table 1: The pharmacokinetic properties of brivaracetam in comparison to levetiracetam.

	Brivaracetam	**Levetiracetam**
Dosage formulations Oral Intravenous	25 mg, 50 mg, 75 mg, 100mg 50 mg/5 mL	250 mg, 500 mg, 750 mg, 1000 mg 500 mg/5 mL; 500 mg/100mL; 1500 mg/5 mL
Bioavailability	100%* (may be delayedwith a high-fat meal)	>95%
Time to peak, median(range)	2 hr (1–4 hrs)	1 hr (1–2 hrs)
Protein binding	15–20%	<10%
Metabolism	Hydrolysis-primarymetabolism Hydroxylation (CYP2C19)-16% Unchanged-9%	34% metabolized(hydrolysis) 66%-unchanged
Involvement of CYP450 enzymes	Yes (CYP2C19)	No
Elimination half-life(t1/2)	7–8 hrs	6–8 hrs
Time for steady-state	2 days of repeated dosing	24–48 hrs of repeateddosing
Clearance	95% via the kidney (8–10% unchanged)	100% via the kidney(66% unchanged)
Dose adjustment in renal failure/dialysis	Not needed	Required (50% supplemental dosefollowing HD
Dosing adjustment in hepatic failure	Reduce dose by 1/3 may be needed	Not needed
Relevant drug-drug interaction	Reduced by co- administration of Rifampin Reduce combined OCPs by20–30%at 400 mg/day	None

Abbreviations: CYP450, cytochrome P450; HD, hemodialysis; OCP, oral contraceptive pills.[15]

Dosage and administration: BRV is available for oral administration (film-coated tablets of 10, 25, 50, 75, and 100 mg or oral solution 10 mg/mL) as well as intravenous administration (injection or infusion, 50 mg/5 mL). A recent crossover study confirmed that these formulations are bioequivalent.[16] The bioavailability of BRV 100 mg intravenous bolus was comparable to that of 50 and 100 mg tablets.

Because of its linear and dose-dependent kinetics, BRV has a favorable pharmacokinetic profile across a wide dose range (10–800 mg/day).[17] BRV is rapidly absorbed after oral administration, with relatively close bioavailability.[18] High-fat meals may cause absorption to be delayed and peak time to be extended by 1 to 3 hours. The median time to peak (Tmax) after oral intake for tablets is approximately 2hours, whereas oral solution shows faster absorption with a max of 37.8 mins.[17]

PERMEABILITY

It is thought that BRV has optimal lipophilicity (logDpH7.4 = 1.04 vs. 0.64 for LEV),[51] that is, high enough to favor cell membrane penetration but below levels associated with water solubility and formulation issues (as observed with phenytoin and most benzodiazepines). This appears to be supported by the in vivo blood-brain barrier permeability measured for BRV in rodents, which not only exceeds that of LEV (0.315 vs.0.015 mL/min/g brain, respectively) but, more importantly, approaches that measured for fast-acting AEDs used in the clinical management of acute seizures.[51]

Metabolism BRV is lipophilic and can enter the brain quickly (LEV).[19] It passes the blood- brain barrier (BBB) passively, without the use of transporters, and binds to SV2A within minutes. BRV is weakly (20%) bound to plasma proteins, with a volume of distribution of 0.6 L/kg. The average elimination half-life of BRV is 7–8 hours and does not vary with dose. After two days of repeated dosing, the steady-state concentration is usually reached. In the liver, BRV is extensively metabolized to three inactive metabolites.[18] It is thought to work by high affinity to a synaptic vesicle glycoprotein called SV2A and inhibiting neurotransmitter release.

Brivaracetam is mostly metabolized by hydrolysis to an inactive chemical compound via amidase enzymes. It is also metabolized to a lesser extent by a minor metabolic pathway involving CYP2C19-dependent hydroxylation. Brivaracetam's FDA-approved drug label states that subjects who are CYPC19 poor metabolizers or are getting treatment that inhibits CYP2C19 may require a dose reduction.[19]

Elimination: Elimination of unchanged BRV and its metabolites occurs via kidneys within 72hrs., with 8.6% of administered dose eliminated unchanged.[56,57] The renal drug clearance approximates 1.68 L/h in healthy subjects.[57] Studies have demonstrated that the pharmacokinetic profile of BRV in elderly and renal impaired subjects is similar to that in healthy subjects.[58] Conversely, severe impairment of liver functions dictates reduction of BRV dose by one third, with a maximal daily dose of 150 mg.[59,60]

Drug-drug interactions: BRV was found to be free of relevant drug-drug interactions, which is an important consideration when assessing the large and complex drug regimens of individuals with chronic epilepsy and other accompanying conditions. BRV neither inhibits nor induces CYPs clinically, nor does it suppress drug transporters, and its metabolism is unaffected by reference AEDs such as felbamate, phenytoin, valproate, lamotrigine, zonisamide, and phenobarbital. When BRV is combined with carbamazepine, the only noticeable effect is a slight increase in carbamazepine-epoxide. This interaction has no safety consequences and does not necessitate dose adjustment. Furthermore, an evaluation of the five regulatory RCTs (N01114, N01193, N01252, N01253, and N01358) revealed that BRV does not affect steady-state plasma concentrations of LEV, CBZ, lacosamide (LCM), lamotrigine (LTG), 10-hydroxycarbazepine, phenobarbital (PB), pregabalin (PGB), phenytoin (PHT), topiramate (ZNS).[20]

Mechanism of Action: SV2A

SV2A is a necessary transmembrane glycoprotein that performs a major function in regulating neurotransmitter release, even though the actual mechanism stays unknown. It has been proposedthat SV2A ought to act as a transporter or modulate exocytosis of transmitter-containing SVs andadjust synaptic function.[21] BRV and LEV bind to the human SV2A protein at closely associated sites, but they have interaction at distinctive binding sites or engage with distinctive conformational states of the protein. BRV has a good deal of extra selective binding with the SV2A protein than LEV; a 13 fold better binding affinity.[22] Several animal research has proven that BRV additionally has a faster penetration, SV2A occupancy, and the onset of movement than LEV. Recently, with the usage of a positron emission tomography study, BRV has been proven to gain therapeutic concentration quicker than LEV (while intravenously administered at healing doses in humans). Similar to LEV, BRV is postulated to exert its anticonvulsant movement via means of binding the SV2A and modulating its impact on neurotransmitter release. Although the info of the way the binding to SV2A brings about its anticonvulsant impact isn't known, It is hypothesized that BRV binding can also additionally stabilize the conformation of SVA2, permitting the protein to satisfy a shielding position throughout seizures. Unlike LEV, BRV no longer modulates inhibitory or excitatory postsynaptic ligand-gated receptors at therapeutically effective brain concentrations, supporting the belief that BRV is a more selective and specific SV2A ligand.[15]

Other Mechanism of actions

i) Voltage-gated ion channels

Indeed, an effective inhibition of sustained repetitive firing is a well-known characteristic of AEDs with a primary mode of action on voltage-gated sodium channels. Another study found that BRV did not affect the amplitude of persistent voltage-gated sodium flows in CA1 neurons. Overall, these findings indicate that the antiepileptic function of BRV is unrelated to voltage-gated sodium channel inhibition.[23] In contrast, at clinically relevant concentrations, LEV inhibits neuronal high voltage-gated calcium flux in rat CA1 hippocampal neurons and superior cervical ganglia neurons, an effect that appears to be selective to the N-type calcium channel.[12]

ii) Excitatory and inhibitory receptors

Except for a weak minor inhibition of the N-methyl-D-aspartate receptor present at supratherapeutic concentrations, BRV has no direct action on inhibitory and excitatory receptors such as a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), glycine, and GABAA.[19] Although it, like LEV, has the ability to block the activity of negative modulators on the two important inhibitory receptors, GABAA, and glycine, the clinical significance of this discovery is unknown.[19] BRV, unlike LEV, does not suppress AMPA receptors.[12]

Adverse Effects

The therapeutic dose range of AEDs, the difference between doses that cause improved management of seizures and those that cause adverse effects, has a significant impact on their clinical utility. Three studies focused on specific irritability and aggression events. Steinhoff et al. performed a prospective observational study in which 33.3 percent of patients switched from LEV to BRV due to tolerability. With the use of BRV, patients experienced less irritability.[24] The reduced incidences of BAEs and psychiatric adverse events in a subset of patients (n = 156) after switching from LEV to BRV were reported in five studies[22,24,25,26,27] (4 retrospective studies and 1 prospective observational research study). Overall, 66.6 percent of patients (weighted mean; range, 33.3–83.0 percent) saw a significant improvement in BAEs after changing from LEV to BRV.[24]

BRV Potency in protection of seizures

BRV has shown higher potency for seizure protection in several animal models of epilepsy[14] and crosses the blood-brain barrier more rapidly than LEV (Finnema et al., 2017).[31]

In study N01114 (NCT00175929), while the primary efficacy analysis did not reach statistical significance at either dose (50 mg/day, 150 mg/day), clear differentiation from placebo was observed in the 50 mg/day group for secondary efficacy parameters (Van Paesschen et al., 2013).[32] The higher dose (150 mg/day) did not appear to provide any additional benefit.

Treatment periods (n = 150), Baseline AED tapering period (n = 147), Monotherapy period (n= 84). Monotherapy studies are generally conducted using a target dose at the higher end of the effective dose range. When these conversion-to-monotherapy studies were designed, results were available from two Phase IIb, double-blind, placebo-controlled studies of adjunctive BRV in adults with focal seizures.

Efficacy

Several double-blind RCTs have reported the safety and efficacy of various doses of oral BRV as adjunctive therapy for uncontrolled focal-onset seizures with or without secondary Generalization.[38]

CLINICAL EFFICACY PHASE I study- Phase I studies The findings of the Phase I study (N01297) in 16 healthy volunteers suggested that the profile of cognitive, subjective, and electrophysiologic effects of BRV is similar to LEV and placebo.[49] In a double-blind, placebo-controlled, parallel-group sequential cohort study of three successive panels of 12 healthy male subjects, BRV was well tolerated at doses of 200–800 mg daily for 2weeks. Additionally, BRV demonstrated a favorable pharmacokinetic profile, characterized by rapid absorption, the volume of distribution limited to total body water, apparent single-compartment elimination, and dose proportionality.[21] In a Phase, I randomized open-label, 5-year crossover study involving 25 patients the bioequivalence of oral and intravenous formulations of BRV was established.[16] In a double-blind, randomized, three-way crossover study that explored the potential pharmacokinetic and pharmacodynamic interactions between ethanol and BRV in 18 healthy males, BRV approximately doubled ethanol effects on psychomotor function, attention, and memory.[50] Therefore, the authors advised against intake of alcohol with BRV and a dose range of 200-800mg to be suggestible as the mentioned evidence.

CLINICAL EFFICACY PHASE II study - In an exploratory, phase IIb, double-blind, randomized, parallel-group, placebo-controlled, dose-ranging study in patients 16–65 years old (N01193) found that adjunctive BRV at a daily dose of 50 mg (but not at 5 or 20 mg doses) was associated with significant reductions in focal seizure frequency per week.[51] In another Phase IIb, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study (N01114), the primary efficacy analysis did not reach statistical significance, however statistically significant differences were observed as compared with placebo on several secondary efficacy outcomes with BRV at a 50 mg daily dose.[52] Hence the author has suggested that BRV plays asignificant role in the reduction of focal seizures and also they have suggested BRV 50mg dose to be effective in the reduction of seizure activity.

PHASE III- as monotherapy Monotherapy Two-Phase III, randomized, double-blind, multicenter, historical-controlled, conversion-to- monotherapy studies (N01276; N01306) were conducted to evaluate the efficacy, safety, and tolerability of conversion to BRV 50 mg/day monotherapy in adults with uncontrolled focal seizures.[58] In this study, patients aged 16–75 years, with 2–40 focal seizures per 4 weeks during an 8-week baseline, and on stable doses of 1–2 ASDs were enrolled. Patients were randomized to BRV 50 or 100 mg/day (3:1) in two equal doses without titration. The treatment period comprised a 1-week BRV add-on, 8-week baseline Anti-seizure drug tapering, and 8- week BRV monotherapy periods. The primary efficacy endpoint was Kaplan–Meier's estimate of the cumulative exit rate due to pre-defined exit criteria at Day 112 (50 mg/day, efficacy population). After randomization of 150 patients, both studies were terminated as interim analysis revealed the studies were unlikely to attain a positive outcome for the efficacy analysis, however, BRV 50 mg/day monotherapy demonstrated an exit rate lower than historical control. In conclusion, BRV 50 mg/day monotherapy demonstrated an exit rate lower than historical control. Authors suggested that results should be interpreted with caution as termination of both the mentioned studies, in which the patient numbers were too low to evaluate the efficacy of BRV monotherapy. These are the first published safety and tolerability data for BRV monotherapy. Monotherapy was well tolerated, with a relatively low incidence of TEAEs, though this should be interpreted with the caution that the majority of common TEAEs were likely to have occurred earlier inthe course of treatment with BRV.

META-ANALYSIS

A meta-analysis was conducted by Francesco Brigo which included Seventeen randomized trials (RCTs) with a sum of 4971 patients. After adjusting for dose effects, indirect comparisons revealed no difference in responder rate or seizure freedom for BRV and Lacosamide, Eslicarbazepine Acetate, or perampanel. High-dose BRV had fewer adverse events than high dose Eslicarbazepine Acetate or perampanel, but there was no difference in withdrawal due to adverse events. This meta-analysis concluded that indirect comparisons show no difference in efficacy between add-on BRV and Lacosamide, Eslicarbazepine Acetate, or Perampanel in focalepilepsy. Results suggest that at the efficacious recommended dose, BRV appears to be more tolerable than Eslicarbazepine Acetate and Perampanel.

Table 1: Summary of Study Designs.

Study number/ clinicaltrials.gov identifier	Type	Patient number: total/active population	Treatment regimen
N01252/NCT00490035	Phase III add-on therapy	400/300	8 weeks baseline assessment, 12 weeks of 20, 50, or 100 mg/day BRV in twice daily (bid) administration without up- titration, 2weeks down-titration
N01253/NCT00464269	Phase III add-on therapy	400/300	8 weeks baseline assessment, 12 weeks of 5, 20, or 50 mg/day
			BRV bid without up-titration, 1week down-titration
N01358/NCT01261325	Phase III add-on therapy	720/480	8 weeks baseline assessment, 12 weeks of 100 or 200 mg/day BRV bid without up-titration, 4weeks down-titration
N01276/NCT00698581	Phase III monotherapy	120/120	8 weeks baseline assessment, 1week BRV add-on, 8 weeks baseline AED down-titration, 8 weeks BRV monotherapy, 6 weeks BRV down-titration andre-conversion to previous therapy. BRV dosed at 50 and 100 mg/day bid during conversion and monotherapy
N01306/NCT00699283	Phase III monotherapy	120/120	8 weeks baseline assessment, 1-week BRV add-on, 8 weeks baseline down-titration, 8 weeks BRV monotherapy, 6 weeks BRV down-titration and re- conversion to previous therapy. BRV dosed at 50 and 100 mg/day bid during conversion and monotherapy

UNIQUE ADVANTAGES OF BRV over LEV:

- BRV has a 13-fold higher affinity for synaptic vesicle glycoprotein (SV2A) than levetiracetam.
- BRV is more potent thus small dose will achieve great efficacy. When small dose is sufficient then the side effects will also be greatly reduced.
- The absence of an AMPA antagonism through BRV maydescribe why changing from LEV to BRV helps to improve BAEs in some PWE (i.e., Events are more AMPA driven in some PWE vs. others) People with epilepsy (PWE) [54]

PMS PHASE IV- Post-marketing studies (Phase IV) A multicenter study aimed to give insights into retention, efficacy, and tolerability in a large cohort of patients with different epilepsy syndromes during the first year of treatment with BRV reported that BRV in broad clinical post marketing use is well tolerated.[70] Efficacy at 3 months was 41.2% (50% responder rate) with 14.9% seizure-free for 3 months and, at 6 months, 40.5% with 15.3% seizure-free. this study concludes that BRV can achieve remarkably high 3- and 6-month responder rates in medical practice, even if in a cohort where 90% of patients had previously been exposed to LEV. This was

surprising because prior LEV use had previously been linked to lower responder rates. Thisstudy also found that an immediate switch from LEV to BRV at a ratio of 10:1–15:1 is feasible.[70] In addition, a recent multicenter retrospective post-marketing study involving 575 patients revealed that the mean reduction in seizure frequency was 36.0%, 39.7% of patients were ≥50% responders and 17.5% were seizure-free at 12 months.[71] Lastly, post-marketing data in 34 children with focal epilepsies and BRV treatment found a 50% responder rate of 47%(29% seizure-free) at 3 months.[72]

Post-marketing studies to determine therapeutic efficacy were conducted by zahnert. et.al, Depending on specific therapeutic decisions and medical reasons, 12/93 patients in this study population received BRV in monotherapy. In this subset of the population, 9/12 (75 percent) of patients achieved seizure-free status. They discovered that BRV treatment can potentially reduce seizure frequency in patients with epilepsies, with a 50% responder rate of 35.1 and 8.8 percent of patients becoming seizure-free for the first time.[55]

Tolerability: BRV has greatly outperformed other previously available antiepileptic medicines in terms of tolerance in animal tests. The therapeutic index (TD50:ED50) of > 57 in rodents for ED50 in the Rotarod test shows that CNS toxic side effects are almost non-existent, even atdosages far exceeding those required for antiepileptic action. This, combined with BRV's excellent antiepileptic effectiveness, has resulted in a notably high BRV retention rate.

BRV has shown good tolerance in animal models, but dose-dependent CNS effects have been observed at high doses (> 100 mg/kg). The protective index of BRV is higher than that of LEV, which is likely due to its action on voltage-gated sodium channels. Acute dose-dependent adverse effects were observed in healthy volunteers with single doses of 80 mg/kg and above in human Phase I investigations.

Overall tolerability was good in placebo-controlled trials, and total adverse event rates in placebo and treatment arms were similar up to 50 mg/day in several studies. Headache (14.8 percent), somnolence (11 percent), dizziness (8.9%), and fatigue (7.8%) were the most common patient complaints, however, none of them were substantially higher than placebo treatment.

Neutropenia was seen; however, it had no correlation with the BRV dose (5 mg BRV 8%, 20 mg BRV 3.8 percent, 50 mg BRV 0%, placebo 1.9 percent). There have been no reports of significant cardiovascular, respiratory, or gastrointestinal adverse effects. There were no notable abnormalities found during neurological examinations, psychometric assessments, vital signs, ECG, EEG, or laboratory tests.

Safety and tolerability

The tolerability data from clinical development programs provide insight into the occurrences of nervousness, anger, and depression. Aggression in people with epilepsy in a clinical development setting under controlled conditions trials. However, while regulatory approval is required, the closed environment and characteristics for these types of trials do not account for the variations that occur in real-world clinical practice.

The Five studies[24,25,26,27,22] observed decreased incidences of BAEs(Behavioral Adverse Events) and psychiatric adverse effects in a subset of patients (n = 156) after a transition from LEV to BRV. Overall, 66.6 percent of patients saw an improvement in BAEs after switching from LEV to BRV. Three studies focused on specific irritability and aggression events. Steinhoff et al. found that 2 of 6 (33.3 percent) patients who switched from LEV to BRV for tolerability experienced less emotional distress with BRV use.[24]

One explanation for the observed trends may be the differences in the primary mechanisms of action of these ASMs(Anti-seizure medication), particularly concerning their antagonism of the mino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, which has been linked to BAEs (such as aggression) observed with ASM treatment.

Levetiracetam, which had the second-highest mean occurrences of irritability in their analysis, is a ligand of synaptic vesicle glycoprotein 2A (SV2A) with some activity toward AMPA-gated currents, which are thought to be associated with the BAEs of LEV.

An exception to this hypothesis could be BRV, which, like LEV, is a selective high-affinity SV2A ligand with no known activity on AMPA. The mechanism(s) by which BRV drives BAEs is unknown because BRV has no activity on other neurotransmitter systems that have been implicated in modulating BAEs, such as serotonin (5-HT) and GABA.

The absence of an AMPA antagonism through BRV may describe why changing from LEV to BRV helps to improve BAEs in some PWE (i.e. Events are more AMPA driven in some PWE vs. others). Alternatively, improvements in BAEs when changing from LEV to BRV could be due to variations in how they interact with the SV2A protein.[50,51] While the precise mechanism(s) (between ASMs) is unknown. We hypothesize that BRV, the more potent SV2A analog, could exert fewer behavioral side effects, as it requires lower doses than LEV.

Switching from LEV to BRV

Although no clinical trial has directly compared BRV with LEV in patients experiencing tolerability problems, the substitution of LEV treatment with BRV is reasonable. Several studies have highlighted the safety

and tolerability of switching from LEV to BRV. In a multicenter retrospective study of 575 patients, among those who switched because of PAEs from LEV therapy (n=53), only 9 (17%) reported PAEs on BRV, and only 3 (5.7%) discontinued because of PAEs.71 In another study, when patients were switched from LEV to BRV due to LEV-induced adverse reactions (mainly PAEs), 57–77% had improved tolerability with BRV.70 Although the occurrence of PAEs during previous LEV exposure predicted poor psycho-behavioral tolerability of BRV treatment, a switch to BRV was shown to alleviate LEV-induced behavioral adverse events.[70,71] An immediate overnight switch from LEV to BRV without titration, at a ratio of 10:1–15:1 is feasible.[70,71] Similarly, in a multicenter study of 61 patients with genetic generalized epilepsy, an immediate switch from LEV to BRV at a 15:1 ratio was feasible without titration.[74] Given that the co-administration of LEV and BRV therapy could theoretically lead to competitive binding of the SV2A ligand and cause severe PAEs; it is generally advised to avoid prescribing BRV in patients concurrently taking LEV.[24]

DISCUSSION

In the past few decades, new ASMs have been developed to achieve, to the greatest extent possible, significant efficacy, favorable pharmacokinetics, and tolerability. Adjunctive BRV proved efficient in decreasing seizure rates in adults with focal-onset seizures in clinical trials atdoses ranging from 50 to 200 mg. mg/day. To a lesser extent, optimal BRV compositions with other ASMs have been investigated.

A study by Fonseca et al. found that Eighty-three-point eight percent (83.8%) of previous levetiracetam (LEV) responders also showed a good response to BRV. In terms of patients who presented LEV-related AEs, AE resolution was observed in 79.8%, particularly concerning psychiatric AEs. A significant improvement of approximately two-thirds of patients being seizure-free. It also has a favorable safety profile, especially in patients who have previously been intolerant to LEV. Brivaracetam may thus be considered a viable therapy of choice for Genetic Generalized Epilepsy (GGE).[53]

Hirsch et al conducted a study in which 102 patients were analyzed for a reduction in adverse effects when they replaced LEV with BRV. 23.8% of patients with a history of LEV use had psychiatric side effects during BRV treatment. Switching to BRV led to a significant improvement in the majority of patients with psychiatric side effects from LEV.[29]

Zahnert et al. conducted a study on a total of 91 patients, 12 (12.9%) received BRV in monotherapy. The mean duration to follow-up was 4.85 months, their study concluded, that BRV could be a promising treatment alternative for epilepsies, particularly for those who have side effects from LEV medication. BRV appears to have increased therapeutic efficacy while also broadening the therapeutic spectrum to allow for more personalized treatment.[55]

Villanueva et al; Their study demonstrated that BRV medication was efficacious and well- tolerated over 12 months, with no unexpected AEs; Most patients had drug-resistant epilepsy, as89.3% had tried 3 AEDs in the past. Brivaracetam was found to be effective in this large, difficult-to-treat population, with 40.0% of patients being responders and 17.2% seizure-free at 6months and 39.7% and 17.5% at 12 months. Psychiatric Adverse Effects were less common than with LEV. Patients with psychiatric illnesses had little difficulty tolerating the medication.

In conclusion, we can say that brivaracetam is the best alternative for quick change from levetiracetam. Future direct head-to-head comparisons will be required to determine BRV's exact position with other ASMs. According to phase II-III studies, BRV has a better safety and tolerability profile. The most common adverse effects, such as somnolence, dizziness, and fatigue, are generally mild to moderate. Long-term experience is still required at this time to rule out particularly serious late-occurring AEs and obtain data on BRV use and safety in pregnancy. The incidence of PAEs in phase III studies has been relatively low, implying that BRV may have a favorable PAEs profile. Emerging evidence suggests that instant conversion from LEV to BRV without titration, at a 10:1-15:1 ratio, may provide additional advantages in terms of tolerability, particularly in patients going to experience PAEs on LEV.

The superior tolerability of BRV over LEV in terms of PAEs is of great interest and necessitates additional research to specify the mechanism.

Monotherapy for the treatment of seizures in epilepsy has a series of advantages over polytherapy, including a lower risk of adverse events, improved adherence, a lower risk of drug- drug interactions, and possibly lower medication costs. The US FDA's new policy allowed for the extrapolation of efficacy in adjunctive therapy to monotherapy use. To assess the efficacy and safety of BRV monotherapy in participants with focal-onset seizures, clinical trials are required. Furthermore, because of its favorable safety profile, BRV should be evaluated as a first-line antiepileptic drug in treatment-naive patients with focal-onset seizures, where it could substitute some older ASMs.

While BRV is only validated for focal epilepsy, preclinical data and its resemblance to LEV suggest that BRV could be an acceptable alternative in primary generalized syndromes.

Preliminary data from clinical studies appear to support this. More research is required to determine the effectiveness of BRV in patients suffering from generalized seizures.

CONCLUSION

BRV has proven to show efficacy in the management of focal and generalized seizures. BRV has more potency for SV2A than LEV which provides the required effectiveness as a monotherapy. BRV has been known to show fewer psychiatric adverse effects when compared to LEV.[5] BRV monotherapy was demonstrating a rare incidence of TEAEs when compared to that of LEV, although BRV monotherapy has shown common treatment of emergent adverse events such as headache, dizziness, somnolence, nasopharyngitis, fatigue.[46] BRV has a fast onset of action, proven tolerability without up-titration.[19] A Cochrane review found that BRV as an add-on has presented a significant number of patients withdrawing from the study due to adverse events although BRV was effective in minimizing the seizure frequency and attaining seizure-free results. A quick replacement from LEV to BRV was safe and is beneficial in avoiding the adverse events encountered in LEV.[55] Brivaracetam monotherapy had demonstrated to be as efficacious as adjunctive therapy with AEDs examined. When transitioning from combination therapy to monotherapy or while starting brivaracetam monotherapy, the same suggested starting dose as for add-on medication should be used. In conclusion, we evidenced that BRV may be a promising option for the treatment of epilepsies, particularly for patients who experience side effects from LEV therapy. BRV appears to have the potential to improve therapeutic efficacy while also broadening the therapeutic scope to allow for more individualized treatment.

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Authors contribution

All the authors have contributed equally.

Conflict of interest

The authors confirm no conflict of interest for this manuscript.

ABBREVATIONS

1. AMPA- a-amino-3-hydroxy-5- methyl-4-isoxazole propionic acid.
2. TEAEs – Treatment Emergent Adverse Events
3. AEs- Adverse Effects
4. BRV- Briveracetam
5. LEV- Levitareacetam
6. PWE -People with epilepsy

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