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ORIGINAL ARTICLE

A prospective, observational, multicentre study to evaluate the efficacy of brivaracetam as adjuvant therapy for epilepsy: The Bravo study

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Abstract

Background: Epilepsy is a persistent tendency to experience epileptic seizures and can lead to various neurobiological disorders, with an elevated risk of premature mortality. This study evaluates the efficacy of brivaracetam adjuvant therapy in patients with epilepsy.

Methods: A prospective observational multicentre study that was conducted in Pakistan from March to September 2022, by using a non-probability convenience sampling technique. The population consisted of 543 individuals with a diagnosis of epilepsy for whom adjunctive brivaracetam (Brivera; manufactured by Helix Pharma Pvt Ltd., Sindh, Pakistan) was recommended by the treating physician. The research sample was drawn from various private neurology clinics of Karachi, Lahore, Rawalpindi, Islamabad and Peshawar. Data originating from routine patient visits, and assessments at three study time points, were recorded in the study case report form.

Results: Across 18 clinical sites, 543 individuals participated, with a mean age of 32.9 years. The most prescribed dosages were 50 mg BD, followed by 100 mg BD. Notably, brivaracetam combined with divalproex sodium was the most prevalent treatment, followed by brivaracetam with levetiracetam. At both the 14th and 90th day assessments, a significant reduction in seizure frequency was observed, with 63.1% of individuals showing a favourable response by day 90. Treatment-naive individuals exhibited higher rates of seizure freedom and response compared with treatment-resistant individuals.

Conclusions: The study demonstrates the effectiveness of brivaracetam combination therapy in epilepsy management, with notable reductions in seizure frequency and favourable clinical responses observed, particularly in treatment-naive individuals.

Keywords: adjunctive brivaracetam, brivaracetam, brivaracetam combination therapy, epilepsy, seizure.

Citation

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Introduction

Epilepsy presents a substantial global health challenge, affecting individuals across all age groups.[1] It contributes significantly to the global disease burden, with over 5 million new cases diagnosed annually and a projected increase in the affected population. This condition resulted in more than 13 million disability-adjusted life years in 2016, comprising 0.5% of the total global burden of disease.[2] Epilepsy is defined by a persistent tendency to experience epileptic seizures and can lead to various neurobiological, cognitive, psychological and social implications. Moreover, individuals with epilepsy face an elevated risk of premature mortality.[1]

Antiseizure medications (ASMs) are the mainstay of treatment for individuals with symptomatic epilepsy.[3] About 47% of those newly diagnosed with epilepsy can achieve freedom from seizures with the first prescribed medication. It is essential for individuals with epilepsy, as well as their families and communities, to understand that seizures can often be managed effectively. With proper use of ASMs, approximately 70% of individuals with epilepsy could potentially achieve seizure freedom. However, it is important to note that around one-third of these individuals may not respond adequately to existing medications.[4,5]

Brivaracetam (BRV) is a carefully developed medication designed with a high affinity for binding to synaptic vesicle protein 2A (SV2A), and a chemical structure resembling that of levetiracetam (LEV).[6] Unlike many other medications, BRV does not interact significantly with drug-metabolizing enzymes or transporters, which reduces the likelihood of clinically important drug interactions. Studies have shown that BRV does not cause notable changes in plasma concentrations, even when used alongside common ASMs like carbamazepine, lacosamide, lamotrigine, LEV, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproate and zonisamide, thereby not requiring dose adjustments.[7]

BRV is approved as an adjunctive therapy in the treatment of focal seizures, with or without secondary generalization, in individuals as young as 4 years old. Its effectiveness and safety have been thoroughly investigated through randomized controlled trials. These trials consistently showed that BRV, at doses ranging from 5 to 200 mg/day, had a notable impact compared to a placebo.[8]

In clinical trials where individuals with drug-resistant focal epilepsy were already taking ASMs, adding BRV led to a reduction in seizure frequency compared to a placebo.[9] Whether used as the initial add-on treatment or as a later addition, BRV showed improvements in seizure frequency for individuals with focal epilepsy. Individuals who started BRV early as an add-on treatment experienced greater and sustained reductions in seizure frequency, and were more likely to continue with the treatment.[10]

Research conducted by Foo et al. suggested that BRV could potentially serve as a beneficial additional treatment for individuals with drug-resistant focal or generalized epilepsies, particularly those who have not responded well to or tolerated LEV therapy in the past.[11] In Europe, BRV was initially authorized as a supplementary therapy for focal onset seizures, whether with or without secondary generalization.[12]

Due to the scarcity of data on how well BRV performs as a supplementary treatment for epilepsy, particularly as either the first or second option, our study sought to address this gap. Our objective was to assess the effectiveness of BRV (Brivera) when used as an adjunctive therapy for individuals diagnosed with epilepsy.

Methods

This study took place across multiple centres in Pakistan from March to September 2022. It was designed as a prospective observational study. We employed a non-probability convenience sampling technique to select participants. The study adhered to the principles of non-interventional trials, that is, participants received treatment as per standard clinical practice and medical indication, without any additional interventions or alterations. Treatment decisions were made based on the physician's discretion and in accordance with marketing authorization.

The study population consisted of 543 individuals with a diagnosis of epilepsy for whom adjunctive BRV (Brivera; manufactured by Helix Pharma Pvt Ltd., Sindh, Pakistan), at dosages of 25, 50 and 100 mg BD, was recommended by the treating physician, in adherence with the local prescribing information/Summary of Product Characteristics of the product, and who provide informed consent for observation. The ethical approval was taken from the Institutional Review Board, King Edward Medical University, Pakistan.

Participant information collected during regular clinic visits, and assessments at three different time points (baseline, day 14, and day 90) was recorded in the study's case report form. The study sample was selected from various private neurology clinics located in Karachi, Multan, Lahore, Rawalpindi, Wah Cantt, Sialkot and Peshawar. The participants were adults of both sexes diagnosed with epilepsy, aged 18 and above, experiencing focal seizures with or without secondary generalization, and willing to

take part in the study. Pregnant or breastfeeding women, as well as individuals with other major neurological problems and contraindications to BRV or any other prescribed combination therapy, were excluded from the study.

We used various statistical methods to analyse the data collected in this study. For continuous variables, like age and seizure frequency, we calculated the mean and standard deviation. For categorical variables, such as sex and treatment response, we presented frequencies and percentages. Additionally, we utilized the χ^2 test to explore the association between seizure episodes, prescribed medications and follow-up visits. Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 15.0 (IBM Corp. Armonk, NY, USA). Statistical significance was determined with a *p* value of <0.05 as significant.

Ethics approval and consent to participate

The research received approval from the institutional ethics committees of King Edward Medical University, Pakistan. Every participant provided their informed consent by signing a consent form. This study followed a prospective, non-interventional approach, adhering to the principles outlined in the Declaration of Helsinki, which did not require registration on ClinicalTrials.gov.

Results

In this study, our objective was to assess the effectiveness of BRV (Brivera) combination therapy for people with epilepsy in a real-world clinical setting by analyzing changes in seizure frequency, instances of seizure freedom, and any worsening of seizures at both the 14th and 90th day follow-up points.

Study sites and demographic characteristics

A total of 543 individuals were enrolled across four clinical sites: Karachi 144 (26.5%), Lahore (26.1%), Rawalpindi and Islamabad 129 (23.8%), and Peshawar 128 (23.6%). The mean age of the participants was 32.9±17.1 years. Amongst the participants, 317 (58.3%) were men and 226 (41.7%) were women. Of the total, 269 (49.5%) were treatment-naive individuals, whilst 274 (50.5%) had treatment-resistant epilepsy. In our study, we observed that the mean duration of epilepsy amongst the participants was 10±2.73 years. Additionally, a considerable proportion (193, 35%) of individuals presented with comorbidities. Furthermore, half of the individuals (272, 50%) were on concomitant medications other than BRV. Notably, a significant percentage of individuals reported a history of psychiatric disorders (109, 20%) or neurological disorders other than epilepsy (136, 25%). Regarding previous ASM exposure, the majority of individuals (326, 60%) had been previously treated with one ASM, whilst 217 (40%) had prior exposure to two or more ASMs. Amongst the various ASMs, LEV emerged as the most commonly prescribed, accounting for 217 (40%) individuals. Carbamazepine and valproate were also frequently used, with respective percentages of 25% (136) and 20% (109).

Seizure frequency and dosage

The mean seizure frequency per month at baseline was 6.19±2.17. The most commonly prescribed dosages were 50 mg BD (twice daily) (117, 47.7%), followed by 100 mg BD (259, 30.7%) and 25 mg BD (167, 21.6%).

Reduction of seizure episodes in combination therapy

The distribution of combination therapies involving BRV at day 14 and day 90 reflects the clinical management of individuals with epilepsy. At both intervals, BRV paired with divalproex sodium emerged as the most prevalent combination, encompassing approximately 52% of individuals. Similarly, BRV combined with LEV demonstrated considerable utilization, comprising around 21% of individuals at both assessments. Other combinations, such as BRV with carbamazepine, lamotrigine, or lacosamide, exhibited varying degrees of usage, accounting for smaller percentages ranging from 3% to 16%. Notably, the distribution of combination therapies remained relatively stable between the two time points, suggesting consistent prescribing patterns over the course of treatment (Table 1).

Table 1. Effect of combination therapy on seizure episodes at 14 and 90 days follow-up.

Adjunctive brivaracetam	Day 14 (*n*=493)	Day 90 (*n*=472)
Brivaracetam with levetiracetam	106 (21.5%)	99 (20.9%)
Brivaracetam with divalproex sodium	257 (52.2%)	248 (52.5%)
Brivaracetam with carbamazepine	77 (15.6%)	75 (15.9%)
Brivaracetam with lamotrigine	17 (3.4%)	14 (3.0%)
Brivaracetam with lacosamide	14 (2.8%)	14 (3.0%)
Brivaracetam with phenobarbital or phenytoin	22 (4.5%)	22 (4.7%)

Clinical response to adjunctive BRV

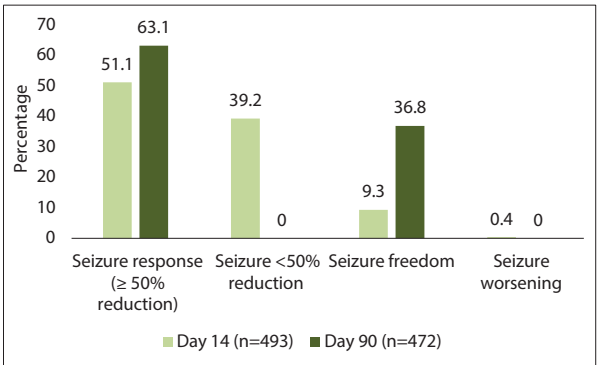
At the 14-day follow-up (n=493), 252 (51.1%) of individuals exhibited a significant seizure response, defined as a reduction of 50% or more in seizure frequency compared to baseline. This response rate increased to 298 (63.1%) at the 90-day visit (n=472), indicating a sustained therapeutic effect over time (p<0.001). Additionally, a notable proportion of individuals achieved seizure freedom, with 46 (9.3%) at day 14 and a remarkable increase to 174 (36.8%) at day 90 (p<0.001). Furthermore, we observed minimal instances of seizure worsening, with only two (0.4%) individuals experiencing increased seizure frequency at the 14-day assessment (Figure 1).

Clinical response in treatment-naive and treatment-resistant individuals

At the 90-day visit, the clinical response to adjunctive BRV was assessed in both treatment-naive and treatment-resistant individuals. In the treatment-naive group (n=269), 53 (19.7%) individuals achieved seizure freedom, whilst an impressive 216 (80.3%) demonstrated a favourable seizure response (≥50% reduction in seizure frequency) (p<0.001). Conversely, in the treatment-resistant group (n=274), a higher proportion of individuals attained seizure freedom, with 148 (54%) experiencing this outcome. However, the number of individuals achieving a seizure response was comparatively lower at 126 (46%) (p<0.001; Table 2).

These results indicate that, whilst both treatment-naive and treatment-resistant individuals can benefit from adjunctive BRV therapy, treatment-naive individuals exhibit a higher likelihood of achieving a favourable response in terms of seizure reduction.

Figure 1. Seizure response to adjunctive brivaracetam: rates of freedom and worsening at 14 and 90 days.



Seizure response: ≥50% reduction in seizure frequency in comparison with baseline seizure frequency.
Seizure worsening: Increase in seizure frequency of >25% in comparison with baseline seizure frequency.

Table 2. Clinical response to adjunctive Brivera (brivaracetam) in treatment-naive and treatment-resistant patients at 90th day visit.

Variable	Seizures freedom *n* (%)	Seizure response *n* (%)	*p* value
Naive (n=269)	53 (19.7%)	216 (80.3%)	<0.001
Treatment resistance (n=274)	148 (54%)	126 (46%)	

p value (two-tail) <0.05 as significant.

Discussion

The findings of this study shed light on the effectiveness of BRV combination therapy in managing epilepsy within a clinical setting. The distribution of individuals across four diverse clinical sites underscores the geographical representation and broad applicability of the study findings. The demographic characteristics of the study population, with a balanced representation of male and female participants, reflect the inclusive nature of the study design.

The average seizure frequency we observed at the beginning of our study is consistent with what other studies have found,[13–18] which helps us better understand the individuals in our study. It seems that prescribing BRV at a dosage of 50 mg BD (twice daily) is common amongst doctors treating individuals with epilepsy, suggesting it is a preferred approach in clinical settings. Previous research has also assessed how effective and well-tolerated adjunctive BRV is when used alongside other treatments for adults with focal onset seizures; these studies, which included six randomized, placebo-controlled trials, found that doses between 50 mg and 200 mg per day had significant positive effects in reducing seizures.[13–18]

The distribution of combination therapies involving BRV highlights the varied treatment approaches adopted by clinicians, with BRV paired with divalproex sodium emerging as the most prevalent combination. The consistency in prescribing patterns over time underscores the stability and reliability of BRV combination therapy in clinical practice.

The significant reduction in seizure frequency and the high rates of seizure response and freedom observed at both the 14-day and 90-day assessments underscore the robust therapeutic efficacy of adjunctive BRV. The

sustained therapeutic effect over time further strengthens the clinical utility of BRV as an adjunctive therapy in epilepsy management. Stefanatou et al. found that, during the initial follow-up visit, 56 (36%) individuals, experienced complete cessation of seizures; additionally, 36% of individuals achieved a reduction of ≥50% in seizure frequency.[19] Our study found a slightly higher rate of seizure freedom compared to a previous study called BRIVA-LIFE, which looked at how effective BRV was in individuals with difficult-to-control focal onset seizures. In that study, after 6 months, about 17.2% of 570 individuals were seizure free, and 40.0% experienced a reduction of ≥50% in seizure frequency.[20] Another study conducted in Europe, which followed 514 individuals over an average of 26.3 months, found similar rates of seizure freedom; 17% of individuals were seizure free and, interestingly, there was not a significant difference in effectiveness between individuals with different types of seizures.[21]

Other studies have found lower rates of seizure freedom when using BRV for focal onset seizures. For example, the EP0077 study, which looked at 199 individuals with focal onset seizures over 6 months, found that only 7.5% were seizure free, whilst 53.6% experienced a reduction of ≥50% in seizure frequency over 28 days.[22] Likewise, a study conducted across multiple centres in the UK examined data from 203 participants who were prescribed BRV.[23] The findings revealed that 8% of individuals achieved seizure freedom after 6 months, whilst 19% experienced a reduction of more than 50% in seizure frequency. Notably, the study found no notable discrepancy in seizure outcomes between participants with focal seizures and those with generalized epilepsy syndromes.

Results from a study carried out at one medical centre involving 101 people with difficult-to-control focal onset seizures showed that, during the 3-month study period, 7% of the participants had no seizures whilst 27.8% noted a decrease of >50% in the frequency of their seizures.[24] In another retrospective analysis, researchers examined the results of 93 individuals who began using BRV therapy as an additional treatment,[25] 90 of whom had focal onset seizures. It was found that 8.8% of the participants achieved seizure freedom, whilst 26.3% experienced a significant reduction of >50% in the frequency of their seizures. Although variations in study design make direct comparisons challenging, these findings offer valuable insights for clinicians in their decision-making process when prescribing BRV in clinical practice.

The BRIVAFIRST study, conducted over a span of 12 months across multiple centres in Italy, centred on adult patients who had been prescribed BRV as adjunctive therapy. The study's findings suggest that adjunctive BRV holds promise as a viable therapeutic option for patients with post-stroke epilepsy.[26] The BRIVAFIRST study, conducted retrospectively across 63 Italian centres, focused on adult patients aged 16 years and older who were prescribed BRV as an add-on treatment. The analysis of BRIVAFIRST data revealed that adjunctive BRV provided clinical benefits for a specific subset of patients with highly active and challenging-to-treat focal epilepsy.[27] In a retrospective, observational, non-interventional study involving adults with focal epilepsy, patients switched to BRV monotherapy after discontinuing background ASMs. Results showed promising rates of seizure freedom, with 72.7% of subjects experiencing seizure freedom at the 6-month follow-up and 58.1% at the 12-month follow-up.[28]

In our study, BRV was frequently paired with other ASMs reflecting common clinical practices in Pakistan. At both assessment intervals, the combination of BRV with LEV demonstrated considerable utilization, comprising around 21% of individuals. The choice of this combination is influenced by the clinical experiences and preferences of healthcare providers in Pakistan. Despite the absence of formal local guidelines for epilepsy management, it is common practice to combine BRV with LEV based on empirical evidence and observed efficacy in clinical settings. This practice reflects the need to tailor treatment to individual patient needs and the real-world efficacy observed by healthcare professionals.

The differential clinical response observed between treatment-naive and treatment-resistant individuals emphasizes the importance of personalized treatment approaches based on patient characteristics and treatment history. The high proportion of treatment-resistant individuals achieving seizure freedom highlights the potential of BRV in addressing unmet therapeutic needs in this patient population. Hu et al. conducted a meta-analysis specifically focused on double-blind randomized controlled trials, comparing new ASMs used as adjunctive therapy for drug-resistant focal epilepsy against either placebo or other ASMs; BRV emerged as the most efficacious and well-tolerated treatment option for drug-resistant focal epilepsy when compared to other newer ASMs.[29]

Conclusion

In this observational prospective study, BRV combination therapy exhibited effectiveness, safety and tolerability in managing epilepsy within a clinical environment. Notably, the majority of individuals demonstrated significant reductions in seizure frequency and favourable clinical responses to adjunctive BRV, particularly evident at the 90-day follow-up. These findings underscore the potential of BRV as an adjunctive therapy in both treatment-naive

and treatment-resistant individuals with epilepsy, providing valuable insights into its clinical utility and patient outcomes.

Future recommendations

Further longitudinal studies with larger sample sizes and longer follow-up durations are warranted to validate and extend the findings of this study. Additionally, investigating the impact of BRV therapy on quality-of-life measures and healthcare utilization amongst individuals with epilepsy could provide a comprehensive understanding of its overall benefits. Furthermore, exploring potential predictors of treatment response and adverse events may facilitate personalized treatment approaches in epilepsy management.

Limitations

Despite the valuable insights gained, this study has several limitations. The observational nature of the study design limits causal inference, and potential confounding variables may influence the observed outcomes. The use of non-probability convenience sampling may introduce selection bias, limiting the generalizability of the findings.

Contributions: FS, BS, and ER contributed to the study design, data collection, and both drafting and critically reviewing the manuscript. AN, SB, JS, HB, MZ, FHM, MWQ and JAS were involved in data collection, analysis, and crafting the results description. ALS, AI, SAb, SAl, SN and KF participated in data collection and contributed to the Discussion section. NM, AA, MIA played a role in the study's design, critical review and finalization of the article. MAK played a role in the assisting with data management, analysis, and writing. All authors have thoroughly reviewed and approved the final manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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