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Review Article

EVALUATING BRIVARACETAM AS AN ADJUNCTIVE THERAPY FOR REFRACTORY FOCAL ONSET SEIZURE: A META-ANALYSIS

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ABSTRACT

Introduction: This study evaluated the safety, tolerability, and effectiveness of Brivaracetam (BRV) as an adjunctive therapy in adults with focal-onset seizures uncontrolled by primary antiseizure medications (ASMs).
Methods: This review systematically incorporated studies from databases including PubMed, ProQuest, The Lancet, EBSCO and the Cochrane Library. Study quality was assessed using the Cochrane Risk of Bias 2 tool. Meta-analysis was conducted with Review Manager 5.4. This study evaluated the efficacy of BRV primarily by the responder rate (patients with ≥50% reduction in seizure frequency) and seizure-free proportion, while assessing safety and tolerability through treatment-emergent and serious adverse events, including treatment discontinuations, with inclusion restricted to studies reporting outcomes over at least 12 weeks.
Result: Seven studies were included, with five qualifying for meta-analysis involving 2,486 patients taking BRV alongside one or more ASMs. The pooled risk ratios for a ≥50% reduction in seizure frequency and complete seizure freedom were 1.83 (95% confidence interval of 1.60 to 2.08) and 7.52 (95% confidence interval of 3.59 to 15.75), respectively. In terms of safety, the use of adjunctive BRV was linked to significantly higher rates of somnolence ($p<0.00001$), dizziness ($p=0.0001$), and fatigue ($p=0.0002$), along with other drug-related treatment-emergent adverse effects (TEAEs) such as headache, irritability and nausea. There was no significant difference ($p>0.05$) between the two groups regarding serious adverse effects (SAEs) or the number of patients who withdrew from the study due to drug-related TEAEs or SAEs.
Discussion: Adjunctive BRV (50-200 mg daily) notably enhanced efficacy outcomes compared to placebo. While drug-related TEAEs occurred more frequently in the BRV group, there were no significant differences in SAEs or withdrawal rates, indicating a favorable safety and tolerability profile consistent with other adjunctive ASMs.
Conclusion: BRV (50–200 mg) is favourable adjunctive therapy for uncontrolled focal-onset seizures.

Keywords: Brivaracetam, Adjunctive therapy, Focal seizure

INTRODUCTION

Epilepsy is a widespread neurological condition that impacts about 50 million people worldwide.[1] It is marked by repeated seizures, which result from abnormal increases in neuronal excitability and a disturbance in the balance between excitatory and inhibitory signals in the brain.[1] Despite the use of standard antiseizure medications (ASMs), 26.6% of patients develop epilepsy that is resistant to medical therapy.[2] Importantly, studies show

that the effectiveness of ASMs decreases with each subsequent trial: 50.5% of patients achieve seizure freedom with their first ASMs, but this rate falls to 11.6% with the second and just 4.1% with the third. After failing two ASMs treatments, the chances of achieving seizure freedom decline sharply, becoming almost negligible after the fourth treatment regimen.[3] The failure to achieve seizure control with additional ASMs is often related to pharmacoresistance mechanisms such as alterations in drug targets, upregulation of drug efflux transporters at the blood–brain barrier, and genetic or structural abnormalities that limit drug responsiveness.[4] As the likelihood of seizure freedom declines sharply after two unsuccessful ASM trials, identifying adjunctive therapies with distinct mechanisms of action becomes essential.[4]

Brivaracetam (BRV) is a newer antiepileptic drug distinguished by its strong and selective binding to synaptic vesicle protein 2A (SV2A), a mechanism that modulates neurotransmitter release. This sets BRV apart from older antiepileptic drugs, which mainly act by targeting ion channels or neurotransmitter receptors.[5] Compared to levetiracetam (LEV), which is also an SV2A ligand, BRV shows a binding affinity that is 10 to 30 times stronger and provides more effective and thorough seizure control in preclinical studies, indicating it may offer improved efficacy for some patient groups.[6] Adults treated with LEV have been shown to experience higher rates of behavioral adverse events (BAEs), such as irritability, agitation, and mood disturbances, compared with those receiving BRV. Clinical studies indicate that BRV is a safe and well-tolerated alternative, associated with fewer and with less severe behavioral side effects than LEV. Notably, switching from LEV to BRV has been associated with a reduction in psychiatric adverse effects, supporting BRV's role as a more tolerable adjunctive therapy for patients with focal-onset seizures.[7]

The purpose of this meta-analysis is to evaluate the efficacy, safety, and tolerability of BRV as an adjunctive therapy specifically for adult patients with refractory focal-onset seizures. Previous studies on BRV have produced conflicting results, which have made it difficult to draw definitive conclusions about its

overall benefits and risks. Therefore, conducting a systematic review and meta-analysis based on an updated literatures is essential to provide a more comprehensive, updated and precise assessment of BRV's effects, helping to clarify its role in the treatment of focal-onset seizures.

MATERIAL AND METHODS

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Eligibility criteria

In accordance with the Population, Exposure, Comparison, Outcome, and Study Type (PECOS) framework, the inclusion criteria were defined as follows:(a) Population: Adults over 18 years old experiencing at least two focal-onset seizures within the four weeks prior to enrollment, despite stable treatment with one or more ASMs; (b) Intervention: BRV used as an adjunctive therapy alongside one or more ASMs as the primary treatment; (c) Comparison: Placebo treatment; (d) Outcome: Objective assessments evaluating the effectiveness, safety, and tolerability of BRV; (e) Study type: Randomized controlled trials (RCTs). The exclusion criteria included: (a) Lack of essential data; (b) Studies conducted in vitro, in vivo, or in silico; (c) Reviews, cohort studies, cross-sectional studies, case reports or series, conference abstracts, book chapters, and commentaries or editorials.

Variables and outcome of interest

Our primary efficacy outcome was the responder rate, defined as the percentage of patients who experienced a 50% or greater reduction in the standardized 4-week seizure frequency, comparing the pre-randomization baseline to the treatment maintenance period. The secondary efficacy outcome was the proportion of patients who remained seizure-free. Regarding the safety of BRV, we analyzed treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Drug-related TEAEs were defined as adverse events that newly appeared or worsened following the initiation of study treatment and were judged by the study investigators to be related to the study

drug. **SAEs** were defined as events that resulted in death, were life-threatening, required or prolonged hospitalization, caused persistent or significant disability/incapacity, or were otherwise considered medically significant by the study investigator.[8] Tolerability of BRV was assessed by examining the frequency of most common adverse events (AEs) and the proportion of patients who discontinued treatment due to TEAEs or SAEs. As ASMs are typically used for long-term management, only studies that reported efficacy, tolerability and safety outcomes over a minimum treatment duration **of** 12 weeks were included.

Search strategy and study selection

An electronic search strategy was designed to cover five databases: PubMed, ProQuest, Lancet, EBSCO, and the Cochrane Library. The following keywords were used for the search: “efficacy”, “adverse effect”, “safety”, “tolerability”, “adjuvant therapy”, “add on therapy”, “brivaracetam”, “brivact”, “nubriveo”, ”brivajoy”, "focal seizure", "refractory seizure". All retrieved studies were imported into the Rayyan platform, where duplicates were removed. Subsequently, titles and abstracts were screened. Each author independently reviewed the titles and abstracts to identify relevant studies, followed by a full-text assessment of potentially eligible articles. Additional exclusions were made after the full-text review. Any disagreements among the authors were resolved through discussion.

Data collection process

The extracted data from the studies included the first author, country of origin, study design, participant characteristics, baseline ASMs, study duration, and the outcomes reported in each study.

Summary measures

The outcomes were evaluated and reported as dichotomous data, showing the risk ratio (RR) with a 95% confidence interval (95% CI) and corresponding p-values. The risk of bias in the included studies was assessed using the Cochrane Risk of Bias 2 (RoB2) tool for randomized controlled trials (RCTs), with findings categorized as low, moderate, or high risk of bias.

Synthesis of results and statistical analysis

Data extraction and synthesis for quantitative analysis were performed using Review Manager (RevMan) version 5.4. Statistical comparisons between groups were conducted with a 95% confidence interval (CI). Subgroup analyses were carried out to assess outcomes across varying doses of BRV. Meta-analyses employed a random effects model, which assumes that treatment effects may vary across different populations and assigns equal weight to each study. Combined risk ratios (RRs) were calculated using the Mantel-Haenszel method. Due to the limited number of included studies, potential publication bias was assessed qualitatively. Study heterogeneity was measured using the I^2 statistic, with values interpreted as follows: below 25% indicating slight heterogeneity, 25%-50% low, 50%-75% moderate, and above 75% high heterogeneity. A p-value less than 0.05 was considered statistically significant.

RESULT

Our systematic review comprised seven studies, of which five were included in the meta-analysis, all meeting the inclusion criteria. Details of the flow diagram are available in Figure 1.

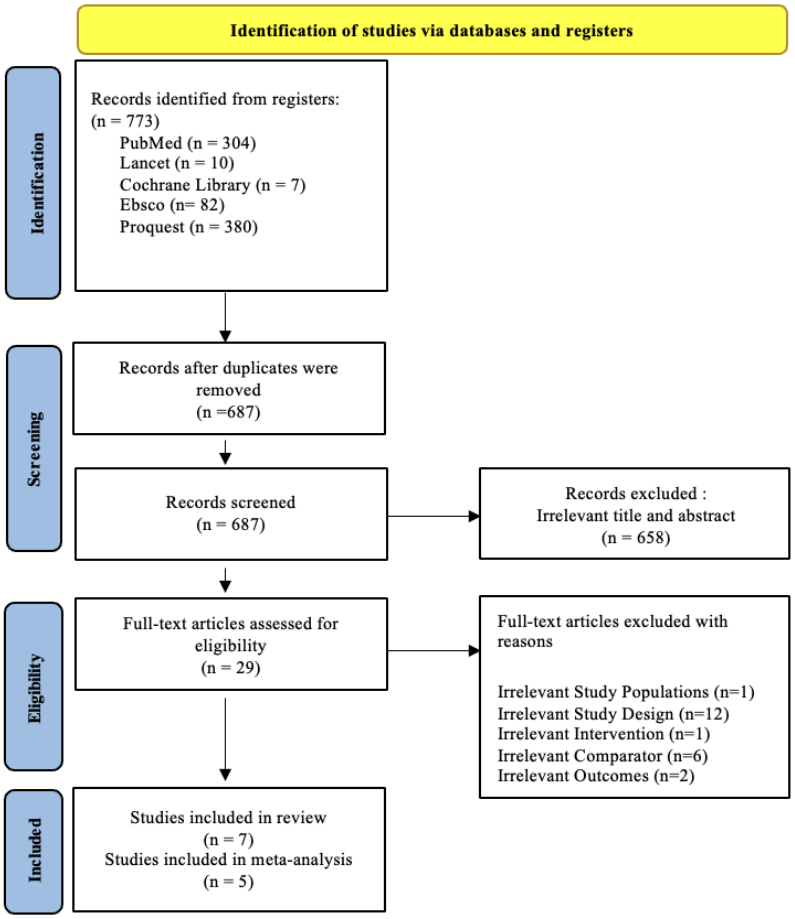

Figure 1. PRISMA 2020 Flow Diagram of Included Studies

Characteristics of the included studies

The five enrolled studies for meta-analysis pooled 2,486 patients.[9-13] Intervention dosage of adjunctive BRV ranged from 20mg/day to 200mg/day. The common ASMs used as main therapy were valproic acid, carbamazepine, levetiracetam, and lamotrigine. The Moseley et al.[15] and Benbadis et al.[14] studies consisted of pooled analyses. The complete characteristics of each study are detailed in **Table 1**.

Quality assessment

The included studies underwent evaluation using the Cochrane Risk of Bias 2 (RoB2) tool for RCT assessment, specifically tailored to RCTs. Results of the risk assessments among included studies are shown in **Figure 2.** Among the seven studies included, three studies were identified as good-quality studies.[10,12-13] The remaining four were of fair quality.[9,11,14-15] Thus, overall, this review included

relatively good quality studies.

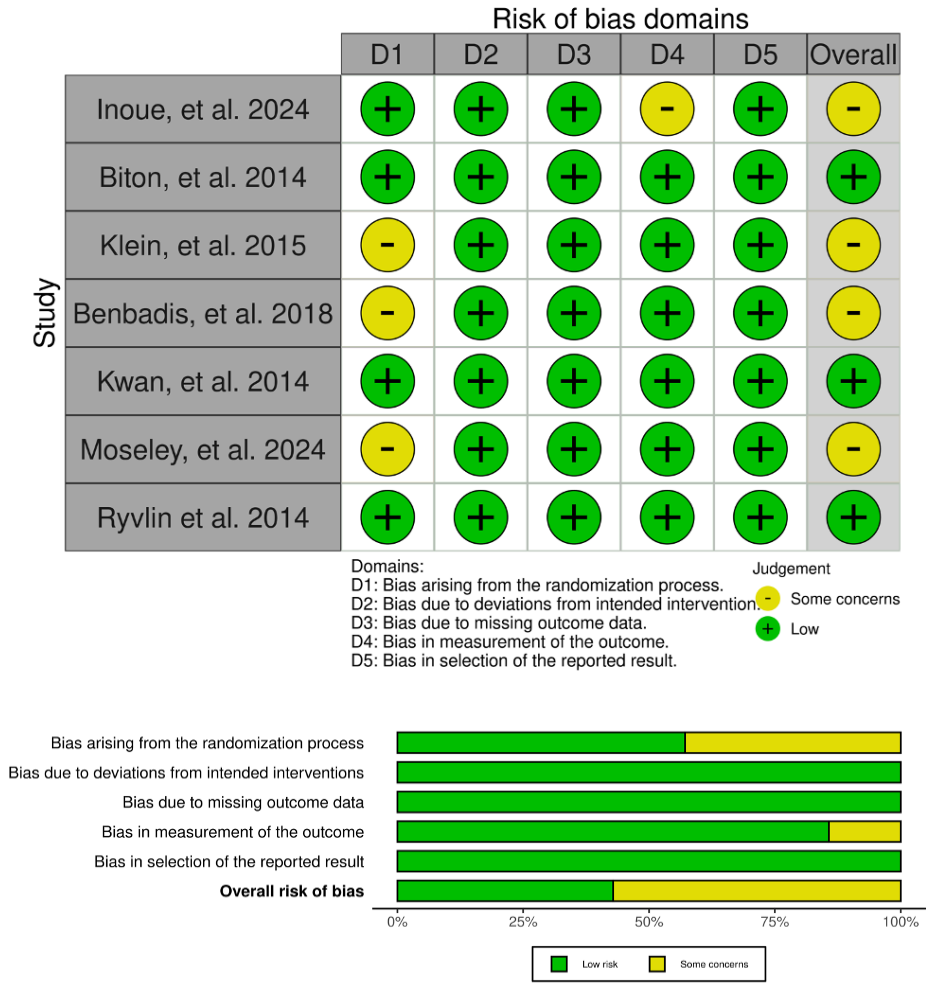

Figure 2. Results of Quality Assessment and Risk of Bias Summary using Cochrane Risk of Bias 2 (RoB2) tool for RCTs

Table 1. Characteristics of the Included Studies.

No	Author, Year	Subject		Intervention	Comparator	Concomitant ASMs	Follow up
		Age	N				
1	Inoue, et al.[9] 2024	34.5 ± 13.0	448	Adjuct BRV (50mg/day, 200mg/day)	Placebo	Valproate (39.7%) Carbamazepine (30.5%) Lamotrigine (22.4%)	12 weeks treatment period
2	Biton, et al.[10] 2014	38.1 ± 12.45	396	Adjuct BRV (5 mg/day, 20 mg/day, 50 mg/day)	Placebo	Carbamazepine (44.9%) Lamotrigine (29.6%) Levetiracetam (19.4%)	12 weeks treatment period
3	Klein, et al.[11] 2015	39.5 ± 12.8	764	Adjuct BRV (100 mg/day, 200 mg/day)	Placebo	Carbamazepine (37.1%) Lamotrigine (25.9%) Valproate (23.2%)	12 weeks treatment period
4	Kwan, et al.[12] 2014	36.5 ± 11.6	431	Adjuct BRV (20mg/day, 50mg/day, 100mg/day, 150mg/day)	Placebo	Carbamazepine (48.3%) Valproate (31.9%) Lamotrigine (24.8%)	16 weeks treatment period
5	Ryvlin et al.[13] 2014	37.2 ± 13.1	399	Adjuct BRV (20mg/day, 50mg/day, 100 mg/day)	Placebo	Carbamazepine (46.5%) Valproic acid (22.4%) Lamotrigine (20.9%)	12-week treatment period
6	Benbadis, et al.[14] 2018	37.3 ± 11.56	342	Adjuct BRV (50mg/day, 100mg/day, 200mg/day)	Placebo	No of concomitant ASMs One (96.5%) Two or more (3.5%)	12 weeks treatment period

7	Moseley, et al.[15] 2024	37.9 ± 12.5	1873	Adjuct BRV (50mg/day, 100mg/day, 200mg/day)	Placebo	Carbamazepine (26.5%) Lamotrigine (17.1%) Valproate (15.6%)	12 weeks treatment period

Outcome on 50% Responder Rate

Four studies were included in this outcome analysis.[9-11,13] Participants receiving BRV have a higher probability to reach a 50% or greater reduction in seizure frequency compared to those receiving placebo (RR of 1.83, 95% CI 1.60-2.08, P < 0.00001). Doses of BRV 20 mg/day might show no significant effect (RR 1.38, 95% CI 0.94-2.01, P = 0.1) whereas higher doses associated with higher ratio to achieve a 50% or greater reduction in seizure frequency (50 mg/day (RR 1.86, 95% CI 1.42-2.43, P < 0.00001), 100 mg/day (RR 1.80, 95% CI 1.42-2.29, P < 0.00001), 200 mg/day (RR 2.09, 95% CI 1.42-3.06, P = 0.0002)). No significant heterogeneity was developed between the trials data (I^2=0%). Fifty percents or greater reduction in seizure frequency outcome in one study by Kwan et al., was not included in this forest plot due to the absence of subgroup analysis based on the dose of brivaracetam (the overall ≥50% responder rate was 30.3% in BRV versus 16.7% in placebo (P = 0.006)).[12] The forest plot is shown in **Figure 3A**.

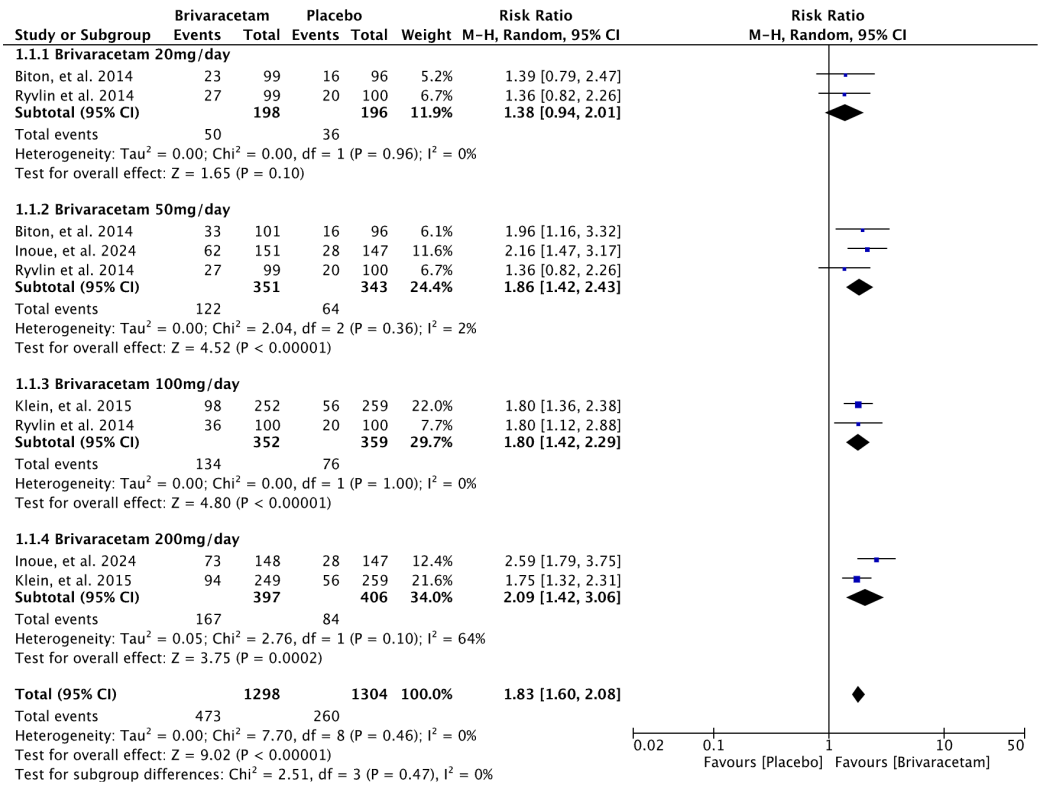

Figure 3A. Meta-analysis forest plot: Pooled RR of responder rate in BRV was compared with placebo.

Outcome on Seizure Free Patients

Four studies were included in this outcome analysis.[9-11,13] Participants receiving BRV indicated a significantly higher rate to acquire seizure freedom compared to those receiving placebo (RR 7.52, 95% CI 3.59-15.75, P < 0.00001). Doses of BRV 20 mg/day might have no significant effect (RR 3.91, 95% CI 0.44-35.07, P = 0.22) while higher doses associated with higher proportion of experiencing seizure freedom (50 mg/day (RR 11.35, 95% CI 1.48-87.03, P = 0.02), 100 mg/day (RR 7.14, 95% CI 2.33-21.85, P = 0.0006), 200 mg/day (RR 8.61, 95% CI 2.32-31.92, P = 0.001)). No significant heterogeneity was established between the trials data (I^2=0%). Seizure freedom outcome in one study by Kwan et al.[12] was not included in this forest plot due to very small incidences of seizure freedom (accounted only 5 out of 323 (1.5%) in BRV versus 0 in placebo (P = 0.337)). The forest plot is shown in **Figure 3B**.

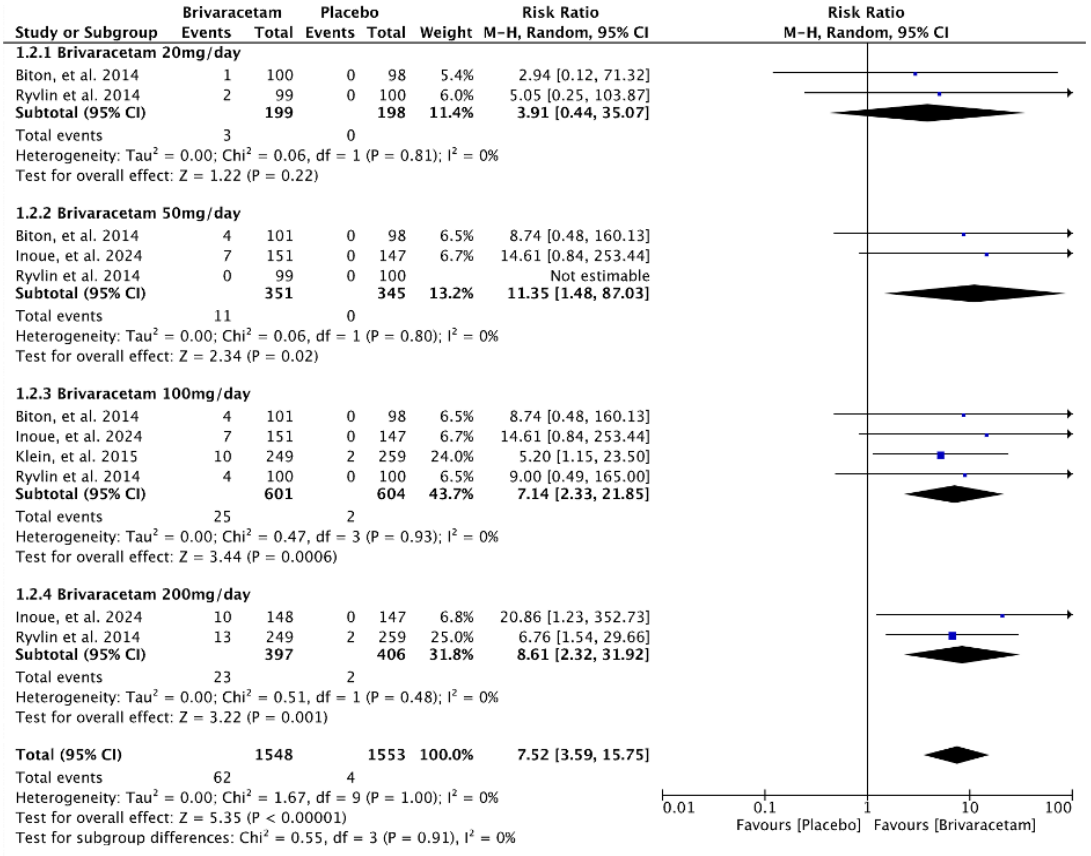

Figure 3B. Meta-analysis forest plot: Pooled RR of seizure-free patients in BRV was compared with placebo.

Outcome on Drug-related TEAE

Four studies were included in this outcome analysis.[9-11,13] Participants receiving BRV indicated a higher rate to experience drug-related TEAE as compared to placebo (RR 1.45, 95% CI 1.22-1.74, P < 0.00001). Doses of BRV 20 mg/day might not be statistically significant (RR 1.01, 95% CI 0.59-1.71, P = 0.98) while higher doses associated with higher proportion of experiencing drug-related TEAE (50 mg/day (RR 1.38, 95% CI 1.12-1.70, P = 0.003), 100 mg/day (RR 1.58, 95% CI 1.26-1.99, P < 0.0001), 200 mg/day (RR 1.98, 95% CI 1.59-2.46, P < 0.00001)) Moderate heterogeneity was established between the trials data (I^2=57%). The forest plot is shown in **Figure 3C**.

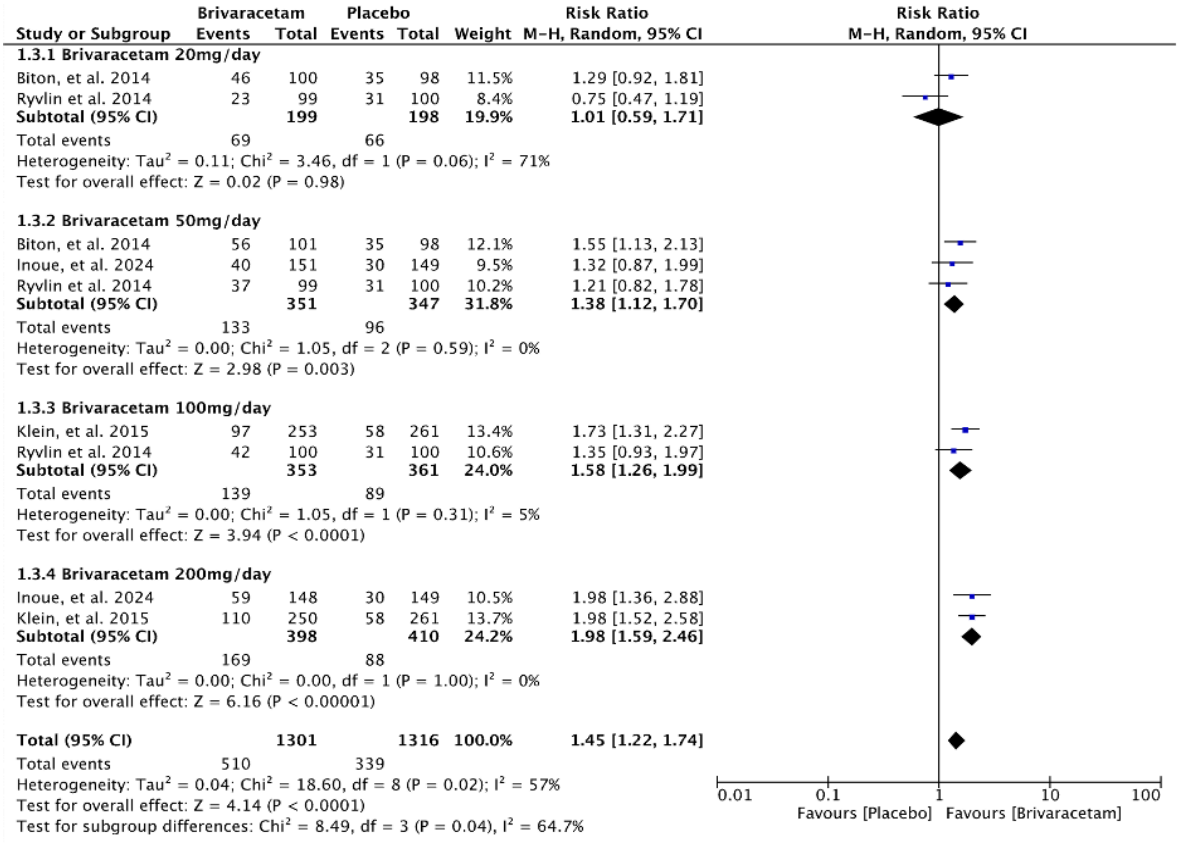

Figure 3C. Meta-analysis forest plot: Pooled RR of drug-related TEAE in BRV was compared with placebo.

Outcome on Serious Adverse Events Four studies were included in this

outcome analysis.[9-11,13] Participants receiving BRV indicated a non-statistically significant SAEs as compared to placebo (RR 1.29, 95% CI 0.89-1.89, P = 0.18). All analyzed doses of BRV might not be statistically significant (20 mg/day (RR 0.87, 95% CI 0.34-2.22, P = 0.78), 50 mg/day (RR 1.46, 95% CI 0.67-3.20, P = 0.34), 100 mg/day (RR 1.30, 95% CI 0.67-2.53, P = 0.44), 200 mg/day (RR 1.47, 95% CI 0.71-3.03, P = 0.30)). No significant heterogeneity was established between the trials data (I^2=0%). The forest plot is shown in **Figure 3D**.

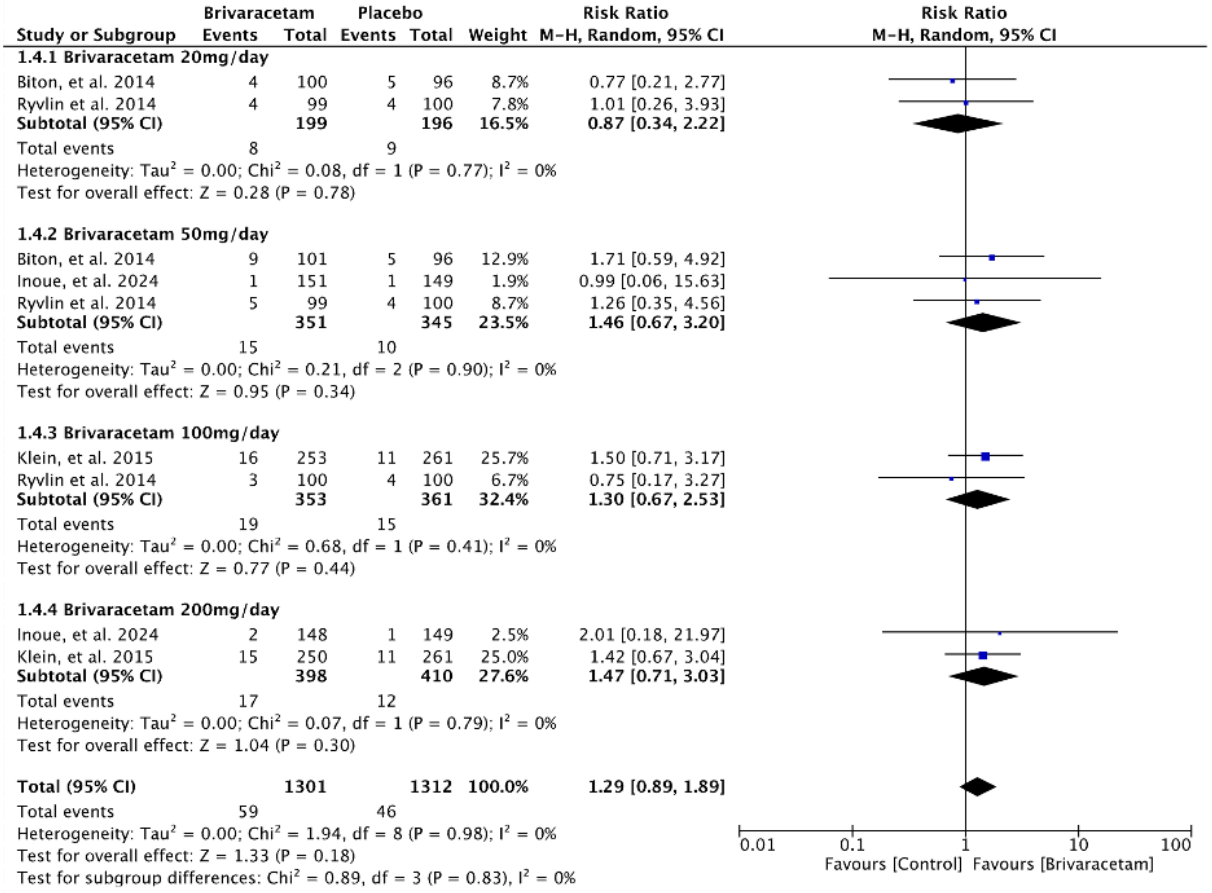

Figure 3D. Meta-analysis forest plot: Pooled RR of SAE in BRV was compared with placebo.

Outcome on Discontinuation due to TEAE and SAE

Four studies were included in this outcome.[9-11,13] The discontinuation rate was non statistically significant between the two groups (RR 1.43, 95% CI 1.00-2.06, P = 0.05). All analyzed doses of BRV might not be statistically significant (20 mg/day (RR 1.31, 95% CI 0.46-3.77, P = 0.61), 50 mg/day (RR 1.15, 95% CI

0.47-2.82, P = 0.76), 100 mg/day (RR 1.89, 95% CI 1.00-3.58, P = 0.05), 200 mg/day (RR 1.25, 95% CI 0.53-2.96, P = 0.62)). All included trials had a minimum treatment duration of 12 weeks, providing adequate time to observe adverse event–related withdrawal. No significant heterogeneity was observed among the studies (I^2 = 0%), supporting the consistency of the findings. These results indicate that BRV is generally well tolerated, with discontinuation rates comparable to placebo across clinically relevant doses.

Adverse Events Analysis

The analysis presented here focuses on the most frequently reported AEs among participants receiving BRV compared to placebo, irrespective of whether they were classified as TEAEs or SAEs. These represent the common effects experienced by patients during treatment and provide clinically relevant insight into BRV's tolerability profile. The prevalence of the most frequent AEs among the BRV-treated participants was: Somnolence 11.7%, headache 10.3%, dizziness 9.25%, fatigue 5.4%, nausea 2.4%, irritability 0.76%. The RRs with corresponding CIs are reported in **Table 2.** Somnolence (RR= 2.05, 95% CI= 1.53–2.75, p<0.00001), dizziness (RR= 1.93, 95% CI= 1.38–2.68, p= 0.0001), and fatigue (RR= 2.46, 95% CI= 1.53–3.97, p= 0.0002) were significantly associated with BRV treatment compared to placebo.

Table 2. Most frequently reported adverse events for add-on Brivaracetam vs placebo

Adverse event	No of Participants (BRV/Placebo)	No of events (BRV/Placebo)	Risk Ratio, M-H, Random (95% CI)	*p* value
Somnolence	1757/729	241/50	2.05 [1.53, 2.75]	<0.00001*
Dizziness	1757/729	190/40	1.93 [1.38, 2,68]	0.0001*
Headache	1757/729	188/68	1.07 [0.65, 1.74]	0.79
Fatigue	1458/580	117/19	2.46 [1.53, 3.97]	0.0002*
Nausea	955/319	44/17	0.83 [0.44, 1.55]	0.56
Irritability	596/198	17/2	2.18 [0.58, 8.19]	0.25

BRV: brivaracetam, *CI:* confidence interval, *M-H:* Mantel-Haenzel

*indicates a significant difference between the BRV group and the placebo group.

DISCUSSION

BRV as an adjunctive therapy for refractory focal-onset seizures demonstrated greater efficacy than placebo, with higher responder rates (≥50% seizure reduction) and seizure freedom outcomes. These results are consistent with previous reviews; however, the present meta-analysis provides an updated evaluation.[16,17] In contrast to earlier analyses, this study incorporates recent phase III randomized controlled trials published up to 2024. Furthermore, efficacy was analyzed across a defined therapeutic range (50–200 mg/day), demonstrating clinically meaningful improvements in seizure control, while 20 mg/day, typically used as a titration or starting dose, showed only a positive but non-significant trend. In addition, this meta-analysis uniquely assessed the tolerability profile of BRV through analysis of treatment discontinuation and most common AEs.

In clinical trials, TEAEs are typically monitored across the entire course of therapy, including both the titration and maintenance phases.[18] Drug-related central nervous system TEAEs are commonly associated with ASMs. BRV was associated with a significantly higher incidence of drug-related TEAEs compared to placebo, particularly somnolence (RR 2.05, 95% CI 1.53–2.75, $p < 0.0001$), dizziness (RR 1.93, 95% CI 1.38–2.68, $p = 0.0001$), and fatigue (RR 2.46, 95% CI 1.53–3.97, $p = 0.0002$) as the most frequently reported TEAE. Pharmacologically, BRV acts as a high-affinity ligand for synaptic vesicle protein 2A (SV2A), modulating neurotransmitter release and reducing neuronal excitability. While this mechanism contributes to its antiseizure effect, it can also lead to CNS depression, which may explain the observed TEAEs such as somnolence, dizziness, and fatigue.[19] Although SAEs were more frequently observed in the BRV group, the difference was not statistically significant (RR 1.29, 95% CI 0.89-1.89, $P = 0.18$).

Consistent results were observed in a study by Meador et al., which found that patients receiving BRV experienced a significantly higher

incidence of drug-related central nervous system TEAEs compared to placebo.[18] However, these adverse events showed a notable decline over time, suggesting the occurrence of habituation. Both the prevalence and incidence of TEAEs significantly decreased over the course of treatment ($p < 0.0001$), with the most substantial reduction observed between week 1 and week 3 ($p < 0.0052$), continuing through to week 12 ($p < 0.0001$).[18] A study by Usui et al. conducted in an Asian population reported similar findings, showing that the incidence of TEAEs and drug-related TEAEs peaked during the first week of treatment and subsequently declined. Discontinuations due to TEAEs were infrequent (1.3% for BRV 50 mg and 2.7% for BRV 200 mg), occurring primarily within the first five weeks and decreasing over time.[20]

In examining previously established adjunctive therapies, Yaohua et al. found that levetiracetam was also associated with a higher rate of drug-related TEAEs compared to placebo, with somnolence (RR 2.26, 95% CI: 1.30–3.93) and hostility (RR 2.33, 95% CI: 1.15–4.70) showing statistically significant associations.[21] Similarly, Halma et al. reported a significant relative risk for overall behavioral side effects in patients taking levetiracetam versus placebo.[22] While both BRV and levetiracetam demonstrate comparable efficacy in seizure control, BRV appears to offer a more favorable tolerability profile. It is considered a safe option due to the absence of a significant increase in serious adverse events relative to placebo. Additionally, the discontinuation rates due to adverse events remain low and comparable between the BRV and placebo groups, supporting its classification as a well-tolerated treatment.

Further supporting this favorable tolerability, a meta-analysis by Zhu et al. systematically evaluated discontinuation rates due to AEs in patients treated with BRV.[18] The analysis revealed no statistically significant difference in the overall risk of treatment withdrawal between BRV and placebo groups (RR 1.18, 95% CI: 0.84–1.65; P = 0.34), nor in withdrawals specifically attributable to adverse events (RR 1.36, 95% CI: 0.91–2.04; P = 0.14).[23] Importantly, subgroup analyses by dose range demonstrated that even higher BRV doses did not significantly increase

the likelihood of discontinuation due to AEs. BRV shows consistent tolerability across dosing regimens, supporting its role as a reliable adjunctive therapy for refractory focal-onset seizures. Its stable discontinuation rate highlights its safety and potential to improve long-term treatment adherence in chronic epilepsy management.

BRV is approved for use in limited countries, including Japan, the United States, the European Union, Canada, Argentina, and Ireland. Consequently, this meta-analysis aims to offer valuable data to healthcare providers and policy makers in regions where BRV is not yet available, shedding light on its effectiveness and safety. This evidence can aid future decisions related to drug approval, formulation of clinical guidelines, and readiness for BRV's potential introduction, ultimately improving epilepsy care in those settings.

This study offers several strengths. It adheres to the PRISMA 2020 guidelines, ensuring a thorough and transparent systematic review and meta-analysis. Additionally, most outcomes showed low heterogeneity, and the risk of bias assessment indicated that the included studies were generally of good quality. However, the study also has limitations, including a limited number of RCTs analyzed. Future research should focus on optimizing BRV dosage regimens, assessing long-term tolerability, and conducting comparative studies of adjunctive BRV versus other antiepileptic drugs. Another limitation of our study is that we did not analyze the correlation between the reduction in AEs and the duration of BRV therapy, nor did we differentiate treatment discontinuations based on the severity of AEs. This additional stratification and time-dependent assessment could have provided deeper insight into the tolerability and safety profile of BRV. Future research should incorporate these analyses to better inform clinical decisions regarding BRV treatment adherence and management of AEs.

CONCLUSION

Adjunctive BRV (50–200 mg per day) significantly improved efficacy outcomes compared to placebo. Although TEAEs were significantly higher in BRV compared to placebo, there were no notable differences in

SAEs or discontinuation rates, suggesting that its safety and tolerability are favourable.

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None

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