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FULL-LENGTH ORIGINAL RESEARCH

Long-term efficacy, tolerability, and retention of brivaracetam in epilepsy treatment: A longitudinal multicenter study with up to 5 years of follow-up

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Abstract

Objective: This study was undertaken to evaluate the long-term efficacy, retention, and tolerability of add-on brivaracetam (BRV) in clinical practice.

Methods: A multicenter, retrospective cohort study recruited all patients who initiated BRV between February and November 2016, with observation until February 2021.

Results: Long-term data for 262 patients (mean age = 40 years, range = 5–81 years, 129 men) were analyzed, including 227 (87%) diagnosed with focal epilepsy, 19 (7%) with genetic generalized epilepsy, and 16 (6%) with other or unclassified epilepsy syndromes. Only 26 (10%) patients had never received levetiracetam (LEV), whereas 133 (50.8%) were switched from LEV. The length of BRV exposure ranged from 1 day to 5 years, with a median retention time of 1.6 years, resulting in a total BRV exposure time of 6829 months (569 years). The retention rate was 61.1% at 12 months, with a reported efficacy of 33.1% (79/239; 50% responder rate, 23 patients lost-to-follow-up), including 10.9% reported as seizure-free. The retention rate for the entire study period was 50.8%, and at last follow-up, 133 patients were receiving BRV at a mean dose of 222 ± 104 mg (median = 200, range = 25–400), including 52 (39.1%) who exceeded the recommended upper dose of 200 mg. Fewer concomitant antiseizure medications and switching from LEV to BRV correlated with better short-term responses, but no investigated parameters correlated with positive long-term outcomes. BRV was discontinued in 63 (24%) patients due to insufficient efficacy, in 29 (11%) for psychobehavioral adverse events, in 25 (10%) for other adverse events, and in 24 (9%) for other reasons.

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Significance: BRV showed a clinically useful 50% responder rate of 33% at 12 months and overall retention of >50%, despite 90% of included patients having previous LEV exposure. BRV was well tolerated; however, psychobehavioral adverse events occurred in one out of 10 patients. Although we identified short-term response and retention predictors, we could not identify significant predictors for long-term outcomes.

KEYWORDS

adverse events, epilepsy, levetiracetam, refractory, seizure, SV2A

1 | INTRODUCTION

Antiseizure medications (ASMs) are typically used in a chronic manner, potentially as components of life-long treatment; therefore, ASM safety, tolerability, and efficacy must be maintained over time. Up to 30% of epilepsy patients are refractory to medical treatment,[1,2] and a refractory disease course has been associated with increased morbidity and mortality, social stigma, reduced employment opportunities, and impaired quality of life for both patients with epilepsy and their caregivers.[3–6] Therefore, the development of new and safe therapeutic options with sustained long-term efficacy remains urgently necessary.

Brivaracetam (BRV) is a high-affinity synaptic vesicle protein 2A ligand that exceeds the binding potential of levetiracetam (LEV) by 10- to 30-fold.[7–12] BRV was approved in 2016 in Europe as an add-on therapy for the treatment of focal seizures in patients aged ≥4 years[13] and was approved in the USA as an adjunctive or monotherapy for the treatment of focal seizures in patients aged ≥4 years (oral formulation only; an intravenous formulation has also been approved for patients aged ≥16 years).[14]

In early randomized controlled trials (RCTs), BRV demonstrated good efficacy for the reduction of focal onset seizures and was associated with a favorable safety profile.[15–17] Later, an open-label, long-term follow-up trial in adult patients with focal epilepsy reported good clinical efficacy (50% responder rate at 12 months) associated with a good safety profile for add-on BRV (doses up to 200 mg), with 50% of patients remaining in the trial at 4 years and 12.4% remaining at 9 years.[18] A pooled analysis, including data from Phase IIb, Phase III, and long-term follow-up studies in adults with focal epilepsy, showed that adjunctive BRV was effective and well tolerated.[19] However, results from clinical trials are difficult to extrapolate to real-life conditions due to the application of strict inclusion and exclusion criteria, the lack of dosing flexibility, and short follow-up periods that do not necessarily represent the realities of clinical practice.[20,21] The results from previous real-life BRV studies are promising, suggesting

> **Key Points**
> - Long-term postmarketing data for brivaracetam in 262 patients showed an overall retention rate of 50.8%
> - At 12 months, the 50% responder rate for brivaracetam was 33.1%, with 10.9% reporting seizure freedom
> - Previous treatment with levetiracetam (90%) did not impact brivaracetam retention or efficacy
> - Levetiracetam treatment failure should not preclude brivaracetam introduction
> - No long-term efficacy predictors could be identified

potential efficacy beyond the treatment of focal seizures, including patients with generalized epilepsy, status epilepticus, or epileptic encephalopathies.[18,22–25] However, most reported studies have been characterized by limited follow-up times, small sample sizes, or a focus on one type of epilepsy.

Our main objective was to describe the efficacy, tolerability, and long-term retention rate of BRV therapy for up to 5 years under real-world conditions among a large, multicenter cohort of children, adolescents, and adults with various epilepsy syndromes. Secondary objectives included the identification of potential predictive factors for BRV therapeutic efficacy and retention.

2 | MATERIALS AND METHODS

2.1 | Study settings and design

This retrospective, multicenter study was performed at university hospitals in Frankfurt am Main, Greifswald, and Münster, in Germany. The study received ethics committee approval; as this was a retrospective study, informed

consent was not required. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were closely followed.[26] This study was not sponsored or funded by any commercial entity.

All epilepsy patients who were started on BRV between February 15, 2016, and November 15, 2016 were included in this analysis. Outcome data between 3 months and 1 year, as of February 2017, were previously published by Steinig et al.[22] All patients who were exposed to at least one dose of BRV were included in the final analysis. The present study reports follow-up data that were collected through February 2021. The use of BRV in patients with status epilepticus has been reported separately.[27] Epilepsy diagnoses were based on the latest definitions proposed by the International League Against Epilepsy and the International Bureau for Epilepsy.[28,29] Information regarding epilepsy syndrome; seizure semiology; seizure etiology; patient demographics; current and previous ASM use, including a detailed history of LEV use; and comorbidities, including the modified Rankin Scale[30] and the Charlson Comorbidity Index score, was provided by the treating physician at each study site.[31] Using a standardized reporting form, the starting, maintenance, and maximum doses of BRV, length of BRV exposure, and BRV withdrawal rates were recorded. Patients were interviewed regarding the occurrence of treatment-emergent adverse events (TEAEs) at each clinic visit, and TEAEs were documented according to established World Health Organization criteria. Patients were typically seen every 3–6 months, and seizure frequency was obtained from medical notes and seizure diaries. Responder rates of 25%, 50%, and 75% were defined as reductions in seizure frequencies of ≥25% but <50%, ≥50% but <75%, and ≥75%, respectively, during follow-up compared with the 3-month baseline. No response was defined as a <25% change in seizure frequency. Seizure increase was defined as a >25% increase in seizure frequency. Responder rates are provided for the first 12 months of treatment and for the final 6 months of treatment. Retention rates are provided for the first 12 months of treatment and for the entire study period. Short-term predictors of response after 3 months have previously been reported.[22]

2.2 | Data entry and statistical analysis

Statistical analyses were performed using SPSS Statistics, version 27.0 (IBM). Retention time on BRV was estimated using Kaplan–Meier survival curves, and the log-rank test was used to conduct comparisons between subgroups. Correlations among categorical variables were evaluated using the Wilcoxon signed-rank test. Binary variables were analyzed using the chi-squared or Fisher exact test,

and continuous variables were assessed by t-test. The Benjamini–Hochberg (BH) procedure was applied to control for false discovery rate, using a p-value of .05.

3 | RESULTS

3.1 | Patients' characteristics at baseline

We report on 262 patients, with a median follow-up of 1.6 years (range = 1 day to 5 years) and a total BRV exposure time of 569 years. The patients' characteristics have previously been published by Steinig et al. covering the first year of BRV use in Germany as of February 2017[22] and are summarized in Table 1. Patients were taking a mean of 2.4 ± .9 ASMs (median = 2, range = 1–6 ASMs) before starting BRV, including 26 (10%) patients taking strong enzyme inducers and 163 (62.2%) patients taking a sodium channel blocker. Patients were exposed to a mean of 4.4 ± 3.8 additional ASMs (median = 4, range = 0–17) prior to the study, without including current ASMs. Only 26 (10%) patients had never been treated with LEV, and 133 (50.8%) were switched to BRV from a mean LEV dose of 2397 ± 1008 mg (median = 2250, range = 500–4000).

3.2 | Treatment with BRV

Treatment with BRV in patients not using LEV at the study onset ($n = 129$) was introduced at a mean dose of 55.8 ± 27.7 mg (median = 50 mg, range = 10–200 mg), with a mean target dose of 128.1 ± 49.2 mg (median = 100 mg, range = 50–200) that was typically achieved within a median of 7 days. In those who were switched from LEV to BRV ($n = 133$), the initial mean BRV dose was 125.2 ± 77.9 mg (median = 100, range = 25–400), with a mean target dose of 175.7 ± 60.0 mg (median = 200, range = 50–400). The LEV to BRV switch was performed at a median ratio of 15:1 (mean = 14.8:1, range = 2:1 to 40:1). The maximal mean BRV dose was 214.8 ± 91.9 mg (median = 200, range = 50–400), with 88 patients (33.6%) exceeding the upper recommended dose of 200 mg. At last follow-up, 133 patients were receiving BRV at a mean dose of 222.0 ± 103.6 mg (median = 200, range = 25–400), with 52 patients (39.1%) exceeding the upper recommended dose of 200 mg.

3.3 | Seizure outcomes during the first year of treatment

After 12 months of BRV treatment, responder rates were available for 160 patients, 79 patients had discontinued

TABLE 1 Clinical characteristics of the studied population (N = 262)

Clinical characteristic	Value
Age, years, mean ± SD[a]	40.0 ± 16.0
Age range, n (%)[a]	
<18 years	9 (3.4)
18–40 years	128 (48.9)
41–64 years	109 (41.6)
>65 years	16 (6.1)
Sex, female, n (%)	133 (50.8)
mRS, median (range)[a]	1 (1–6)
CCI, median (range)[a]	0 (0–4)
Epilepsy syndrome, n (%)	
Idiopathic generalized epilepsy	19 (7)
Symptomatic or cryptogenic focal epilepsy	227 (87)
Symptomatic generalized epilepsy	8 (3)
Unknown epilepsy syndrome	8 (3)
Etiology, n (%)	
Cerebrovascular	21 (8.0)
Dysplasia/hippocampal sclerosis	46 (17.6)
Tumor	17 (6.5)
Other symptomatic causes	60 (22.9)
Idiopathic/cryptogenic	106 (40.5)
Not available	12 (4.6)
Age at epilepsy onset, years, mean ± SD/ median (range)[b]	18.4 ± 17.6/14 (.1–80)
Epilepsy duration, years, mean ± SD/ median (range)[a,b]	21.6 ± 14.7/20 (.1–71)
Number of ASMs, mean ± SD/median (range)[a]	2.4 ± .9/2 (1–6)
1, n (%)	45 (17.2)
2 or more, n (%)	217 (82.8)
Previously failed ASMs, mean ± SD/ median (range)[c,d]	4.4 ± 3.8/4 (0–17)
0–3, n (%)	128 (48.9)
4 or more, n (%)	130 (49.6)
Seizure frequency per month in the 3-month baseline period, mean ± SD/median (range)	
Overall seizure frequency	25.0 ± 47.9/7 (0–405)
GTCS, n = 113	4.4 ± 7.8/1.5 (.3–60)

Abbreviations: ASM, antiseizure medication; CCI, Charlson Comorbidity Index; GTCS, generalized tonic–clonic seizures; mRS, modified Rankin Scale.

[a]At brivaracetam start.

[b]Seven patients with missing data.

[c]Four patients with missing data.

[d]Current ASMs not included.

BRV, and 23 patients were lost to follow-up. A 50% response rate (50% or greater seizure reduction) was reported by 79 patients (33.1%, 79/239), including 26 patients reporting seizure freedom (10.9%, 20 becoming and six remaining seizure-free as compared to baseline). An additional 15 (6.3%) patients had between 25% and <50% reductions in seizures. In 58 (24.3%) patients, no change in seizure frequency was reported, and eight (3.3%) patients reported increased seizure frequencies (Figure 1A).

We then compared the patients with >25% seizure reductions with those who reported either no clinical response, BRV discontinuation, or seizure increase or were lost to follow-up. A total of 125 (47.7%) patients showed >25% seizure reductions during the first 3 months of follow-up, and 94 (35.9%) patients presented with >25% seizure reduction after 12 months. During the short-term follow-up period (3 months), the use of fewer concomitant ASMs (1 vs. 2 or more) and switch from LEV were significantly associated with a better clinical response (hazard ratio [HR] = 1.46, 95% confidence interval [CI] = 1.12–1.90 and HR = 1.36, 95% CI = 1.05–1.76, respectively).[22] During the long-term follow-up period (12 months), none of the investigated parameters was significantly correlated with long-term outcomes (Table 2).

3.4 | Terminal seizure outcomes during the last 6 months of follow-up

Terminal seizure outcome data for the last 6 months was available for 200 patients, whereas 55 (21.0%) patients discontinued BRV treatment before 6 months and seven (2.7%) were lost to follow-up. Overall, 51 patients reported seizure freedom (51/200, 25.5%), an additional 31 (15.5%) patients reported 75%–99% seizure reductions, 29 (14.5%) patients reported 50%–74% seizure reductions, and 11 (5.5%) patients reported 25%–49% seizure reductions. No changes were reported by 61 (30.5%) patients, and 17 (8.5%) patients described increases in seizure frequency (Figure 1B).

A >25% seizure reduction was reported by 122 (46.6%) patients. Age, sex, epilepsy syndrome, epilepsy etiology, epilepsy duration, seizure frequency, seizure semiology, the transition from LEV, maximal BRV dose, and the number of ASMs used at the time of BRV introduction were not significantly correlated with seizure outcomes. Prior therapy with LEV was associated with worse clinical response (response rate = 44.2% vs. 69.2%, p = .021, with significance lost after BH correction for multiple comparisons). The number of previously failed ASMs (dichotomized as 1–3 vs. >3) was significantly lower in patients with >25% seizure reduction (response rate = 53.9% vs. 40.0%, p = .034, with significance lost after BH correction).
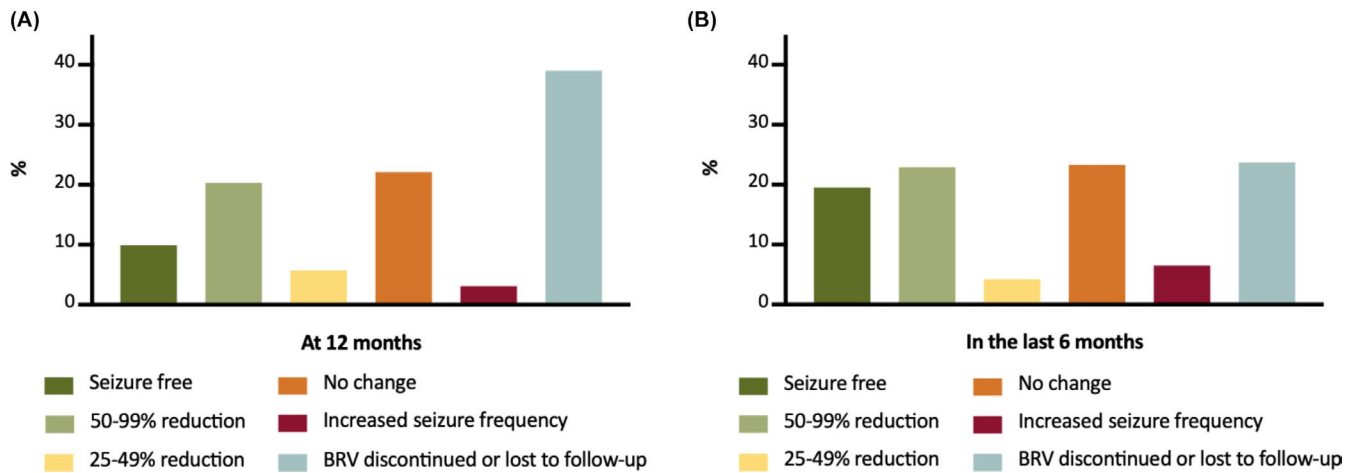
FIGURE 1 Seizure outcomes at 12 months (A) and during the last 6 months of follow-up (B).

3.5 | Retention and discontinuation of BRV

The median BRV retention time was 1.6 years (range = 1 day to 5 years), resulting in a total BRV exposure time of 6829 months (569 years). The probability of remaining on BRV was 61.1% (160/262 patients, 23 were lost to follow-up) after 12 months. The retention time was defined as the probability of remaining on BRV treatment and was assessed using Kaplan–Meier survival curves for all patients (Figure 2A), depending on the switch from LEV to BRV (Figure 2B), the number of previously failed ASMs (Figure 2C), and the number of concomitant ASMs used at the time of BRV initiation (Figure 2D). The retention rate did not differ significantly between groups stratified according to LEV to BRV switch (log-rank $p = .31$), the number of previously failed ASMs (log-rank $p = .88$), or the number of concomitant ASMs at BRV initiation (log-rank $p = .54$).

At the last follow-up, BRV was discontinued in 129 (49.2%) patients, resulting in an overall retention rate of 50.8% for the entire study period. BRV was discontinued due to insufficient efficacy in 63 (24.0%) patients, psychiatric adverse events in 29 (11.1%, 10 of these were switched from LEV due to psychobehavioral adverse events) patients, other adverse events in 25 (9.5%) patients, and other reasons in 24 (9.1%) patients. The reasons given for BRV discontinuation (not mutually exclusive) are summarized in Table 3.

4 | DISCUSSION

Our study reflects 5 years of real-world experience with BRV in a large cohort of 262 patients who were started within the first 9 months after BRV became available on the market in Germany.

After 12 months of BRV use, 33.1% of patients reported >50% seizure reduction, including 10.9% of patients reporting seizure freedom (20 becoming seizure-free and six remaining seizure-free as compared to baseline). These results are consistent with the initial RCTs examining BRV efficacy.[15–17,32] A pooled analysis from three RCTs reported responder rates of 34.2%, 39.5%, and 37.8% with BRV doses of 50, 100, and 200 mg, respectively.[32] The pooled analysis included data from Phase IIb, Phase III, and long-term follow-up studies, which described a similar responder rate as the present study (the overall responder rate was 48.7%); however, the pooled analysis reported lower rates of seizure freedom after ≥6, 12, 24, and 60 months: 4.9%, 4.2%, 3.0%, and 3.3%, respectively.[19] A later open-label, long-term follow-up trial reported a 55.6% overall 50%-responder rate, with 20.3% of patients reporting seizure freedom after 12 months.[18] Interestingly, the BRV efficacy is similar to those reported in long-term follow-up trials using other ASMs[33,34] and appears to be comparable to that described in a previous retrospective study of BRV.[35,36] Few studies investigating BRV efficacy in the real-world setting have reached 12 months of follow-up. A retrospective Spanish study, which included adult patients with focal epilepsy, reported an overall response in 40% of patients, with 17.2% reporting seizure freedom after 12 months.[36] These discrepancies might be due to differences in study design. In our study, the percentage of responders was reported relative to the entire population who started BRV (intention to treat analysis). In the Villanueva study, efficacy was assessed for the period between two visits (3 months),[36] whereas, in our study, the entire 12-month period was considered. Comparisons between studies should be made with caution due to differences in the studied populations, differences in the definition of efficacy, and differences in the assessed drug regimens. RCTs and most long-term follow-up trials and retrospective

TABLE 2 Clinical characteristics of patients with and without response to BRV at 12 months

Characteristic	>25% seizure reduction, n = 94, 35.9%	No efficacy, n = 168, 64.1%	p/OR (95% CI)
Sex, female, n (%)	48 (51.1)	85 (50.6)	1/1.0 (.6–1.7)
Age, years, median (IQR)[a]	37.5 (26.3–52.0)	38.5 (26.0–54.0)	.3344
<18 years, n (%)	3 (3.2)	6 (3.6)	1/.9 (.1–4.3)
18–40 years, n (%)	48 (51.1)	80 (47.6)	.6085/1.1 (.7–1.9)
41–65 years, n (%)	42 (44.7)	67 (39.9)	.5138/1.2 (.7–2.1)
>65 years, n (%)	1 (1.1)	15 (8.9)	.01288/.1 (.003–.7)
Epilepsy duration, median (IQR)[a]	20 (9–30)	20 (10–31.75)	.6216
Epilepsy syndrome, n (%)			.4809
Idiopathic generalized epilepsy	6 (6.4)	13 (7.7)	.8065/.8 (.2–2.4)
Symptomatic or cryptogenic focal epilepsy	83 (88.3)	144 (85.7)	.7054/1.3 (.6–3.0)
Symptomatic generalized epilepsy	4 (4.3)	4 (2.4)	.463/1.8 (.3–10.0)
Unknown	1 (1.1)	7 (4.2)	.2654/.2 (.01–2.0)
Etiology, n (%)[b]			.2482
Cerebrovascular	5 (5.4)	16 (10.1)	.242/.5 (.1–1.5)
Dysplasia/hippocampal sclerosis	13 (14.1)	33 (20.9)	.2362/.6 (.3–1.3)
Tumor	6 (6.5)	11 (6.9)	1/.9 (.3–2.9)
Other symptomatic causes	28 (30.4)	32 (20.3)	.09071/1.7 (.9–3.2)
Idiopathic/cryptogenic	40 (43.5)	66 (41.8)	.7925/1.1 (.6–1.9)
Seizures[a]			
Seizure frequency per month, median (IQR)	6.25 (2.5–28.75)	8 (2–28)	.379
Primary GTCS, yes, n (%)	5 (5.32)	15 (8.9)	.341/.6 (.2–1.7)
Focal seizures, n (%)	69 (73.4)	132 (78.6)	.363/.8 (.4–1.4)
Absence, yes, n (%)	4 (4.3)	2 (1.2)	.1918/3.7 (.5–41.3)
Myoclonic, yes, n (%),	3 (3.2)	5 (3.0)	1/1.1 (.2–5.7)
LEV status, n (%)			
Switch from LEV to BRV	45 (47.9)	88 (52.4)	.5207/.8 (.5–1.4)
Previous exposure to LEV[c]	79 (85.0)	154 (92.8)	.05328/.4 (.2–1.1)
Previously failed ASMs, median (range)[a]	4 (0–15)	4 (0–17)	.9168
0–3, n (%)	46 (49.5)	82 (49.4)	1/1.0 (.6–1.7)
4 or more, n (%)	47 (50.5)	83 (50.6)	
Number of concomitant ASMs, median (range)[d]	2 (1–5)	2 (1–6)	.8939
1, n (%)	14 (14.9)	31 (18.5)	.499/1.3 (.65–2.57)
2 or more, n (%)	80 (85.1)	137 (81.5)	
BRV maximal dose, median (range)	200 (50–400)	200 (50–400)	.3415

Note: "No efficacy" was defined as any increase in seizure frequency, unchanged seizure frequency, loss to follow-up, or BRV discontinuation.

Abbreviations: ASM, antiseizure medication; BRV, brivaracetam; CI, confidence interval; GTCS, generalized tonic–clonic seizures; IQR, interquartile range; LEV, levetiracetam; OR, odds ratio.

[a]At the time of BRV initiation.

[b]Three patients with missing data.

[c]Two patients with missing data.

[d]Not including BRV.

studies tend to focus on patients with focal epilepsy using fixed BRV dose regimens. By contrast, our study included patients of all ages and included those with generalized epilepsy.

Efficacy did not differ according to seizure semiology or epilepsy syndrome. Previous reports have suggested that BRV could be effective for treating generalized epilepsy, with good responses especially demonstrated in
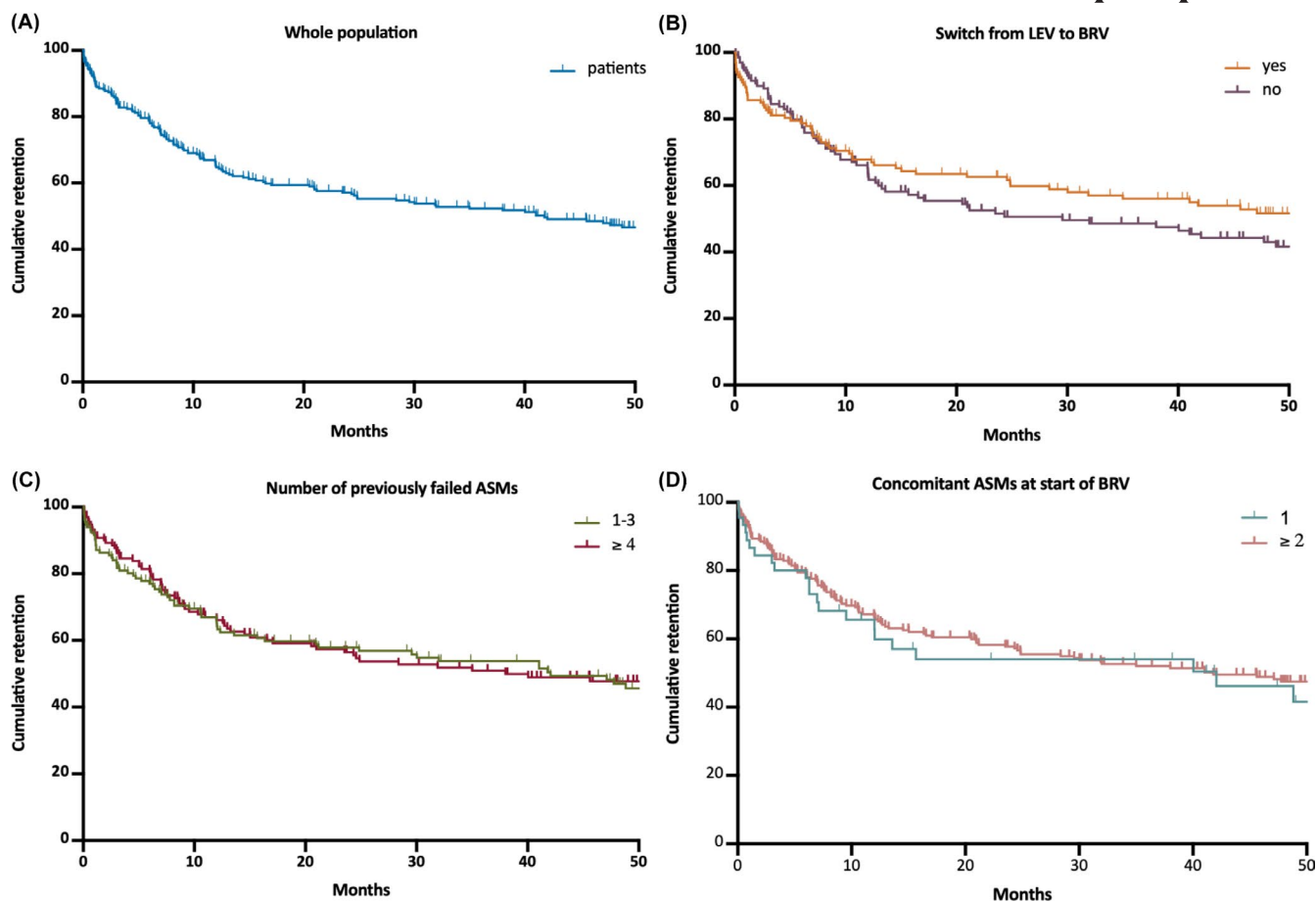
FIGURE 2 Retention rate of brivaracetam (BRV) in the complete cohort (A), in patients switched from levetiracetam (LEV) to BRV (B), and according to the number of previously failed antiseizure medications (ASMs; C) or concomitant ASMs at start of BRV (D)

patients with juvenile myoclonic epilepsies.[23,37] However, the number of reported patients treated with BRV for generalized epilepsy remains very low, and additional studies focusing on this population remain necessary. In addition, the number of elderly patients with epilepsy is increasing, and data concerning this population, which is often excluded from RCTs, are also necessary.[38] BRV showed a significant reduction in efficacy among older adults (>65 years) in the present study; however, significance was lost after correction for multiple comparisons. By contrast, post hoc analyses of Phase III studies suggested that BRV might represent a promising treatment for older adults.[39]

A previous short-term study investigating the same population described in the present study at the 3-month follow-up time point reported that switch from LEV was associated with reduced BRV efficacy,[22] whereas in this long-term follow-up study, neither previous treatment with LEV nor switch from LEV was associated with changes in BRV efficacy or retention. Previous data suggest that BRV is effective and well tolerated in patients switched from LEV.[40,41] The reduced efficacy observed after 3 months in patients switched from LEV might be due to the BRV target dose being initiated almost immediately in those with previous LEV treatment, whereas those patients who were not switched from LEV were introduced to BRV using a slow titration period. Nonresponders might also be distinguished earlier among patients who switch from LEV compared with those without previous LEV treatment. Interestingly, a post hoc analysis of pooled data from RCTs reported a lower efficacy not only in LEV-exposed patients but also in patients treated with carbamazepine, topiramate, and lamotrigine.[42]

These results suggest that previous ASM exposure is associated with BRV failure, regardless of their underlying mechanisms of action. In our cohort, the use of fewer concomitant ASMs and BRV initiation in patients not currently taking LEV were associated with better outcomes after 3 months.[22] This is not surprising, as clinical practice shows that the chance of success is always higher in patients who get their first, second or third ASM. However, we were unable to identify predictors of long-term efficacy and cannot provide strong guidance for clinicians to assist in the determination of which patients will benefit from BRV use.

TABLE 3 Reasons for brivaracetam discontinuation (n = 129)

Reason	n	%
Insufficient efficacy	63	48.8
TEAEs		
Psychobehavioral	29	22.5
Depression	6	
Irritability	5	
Psychotic symptoms	2	
Anxiety	1	
Suicidal ideation	1	
Unspecified	14	
CNS-related	25	19.4
Confusion	2	
Somnolence	8	
Dizziness	8	
Sleep disorders[a]	2	
Walking difficulty	3	
Ataxia	1	
Word-finding difficulties	1	
Others	14	10.9
Nausea	3	
Loss of appetite	2	
GI problems[b]	7	
Pain	2	
Allergic reaction	1	
Other reasons	24	18.6
Unknown	7	
Cost/medication access issues	5	
PNES	1	
Death or palliative care	3	
Child planning	1	
Treatment adaptation[c]	6	
Pregnancy	2	

Abbreviations: CNS, central nervous system; GI, gastrointestinal; PNES, psychogenic nonepileptic seizures; TEAE, treatment-related adverse event.

[a]Insomnia and nightmares.

[b]Five cases of diarrhea and two cases of constipation.

[c]Phenytoin intoxication, seizure-free, treatment simplification.

The retention rate was 61.1% after 12 months, with an overall retention rate of 50.8%. One systematic review that compared BRV retention rates in open-label extension studies with retention rates for other ASMs reported similar findings.[43] The 52-week retention rate for BRV was 69.8%, whereas the retention rates for other ASMs at the same time point (eslicarbazepine, gabapentin, lacosamide, LEV, oxcarbazepine, perampanel, pregabalin, topiramate, and zonisamide) ranged between 63.3% and 66.7%.

One study investigating BRV prescriptions in a real-world setting reported a slightly higher 12-month retention rate (70.4%) than that found in this study.[36] This discrepancy could be due to differences in the patients' baseline characteristics and the study design. As previously described, the BRV retention rate appears to decline gradually over the first year (79.4% at 3 months, 75.8% at 6 months, and 61.1% at 12 months), followed by a relative stabilization period after 12 months.[44–46] Initial efficacy, often referred to as the honeymoon period, is a well-known phenomenon, especially among patients with drug-resistant epilepsy.[47] A similar finding was observed by our group, with a 41.2% responder rate (including 14.9% reporting seizure freedom) at 3 months, but only a 33.1% responder rate (including 10.9% reporting seizure freedom) at 12 months. Our results emphasize that BRV is associated with a good retention rate (similar to other ASMs), even among a population that includes >90% of patients with a history of LEV treatment. The retention rate did not differ between the groups stratified according to prior LEV treatment, the number of failed ASMs, or the number of concomitant ASMs, further supporting that LEV failure should not preclude BRV introduction.

During this long-term follow-up study, BRV was generally found to be safe and well tolerated. The most commonly reported adverse events were somnolence, dizziness, and psychobehavioral side effects, similar to those described in previous trials.[15–18,22,23,37] The mechanism driving the psychobehavioral side effects of BRV remain unclear, although BRV activity on neurotransmitter systems, such as the γ-aminobutyric acid and serotoninergic systems, has been postulated.[48,49] Unlike LEV, BRV does not have α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonistic activity, which has been hypothesized as a contributing mechanism for the psychobehavioral adverse events observed in patients treated with LEV[49] and could explain why transitioning from LEV to BRV can improve psychobehavioral symptoms in some patients. BRV was discontinued due to adverse events in 20.6% of our patients, which is a higher proportion than described in the previous literature[16,17,22,23,36,37,41,50] and may be due to the real-world setting of our study, which was not limited by strict, a priori patient selection. When compared with other ASMs that are prescribed in a similar setting, BRV appeared equally or less disabling (discontinuation due to adverse events: 30% for zonisamide, 46% for pregabalin, and 19% for LEV).[44] As previously reported, the lack of efficacy was the most commonly reported reason for BRV treatment discontinuation.[40]

Several limitations of this study should be acknowledged. First, this study is limited by the risks inherent to any study with a retrospective design, including the potential for relevant information to be missing from records, the lack

of randomization, and variations in follow-up timing. The lack of a control group prevents the drawing of conclusions regarding BRV efficacy relative to other ASMs. BRV doses were not standardized in the present study, and 39.1% of patients exceeded the recommended dose of 200 mg. However, this real-world setting, which involved the uptitration of BRV doses at the treating clinician's discretion, represents one of the strengths of our study, as it reflects real-life clinical practices. Furthermore, BRV doses were not associated with retention or efficacy, suggesting that bias associated with BRV use beyond the recommended dose is unlikely. In addition, only few children were included, so that detailed information cannot be provided for the pediatric publication; later performed studies have answered this question.[51] Further prospective studies, including the evaluation of scales measuring quality of life and psychosocial inventories, are warranted to fully evaluate the long-term efficacy and tolerability of BRV.

5 | CONCLUSIONS

This study confirms that add-on BRV was well tolerated in a real-world setting and improved long-term seizure control in patients with various epilepsy syndromes. The observed responder rates within the first 12 months of BRV therapy in this study were in line with those reported by prior RCTs, and the overall high retention rate of 50.8% underlined the good efficacy and tolerability of BRV. These findings were observed in a cohort in which 90% of patients had previous LEV exposure, suggesting that LEV treatment failure should not preclude BRV introduction.

CONFLICT OF INTEREST
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