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FULL-LENGTH ORIGINAL RESEARCH

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Brivaracetam substituting other antiepileptic treatments: Results of a retrospective study in German epilepsy centers

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Abstract

Objective: To evaluate the success of initiation of adjunctive brivaracetam in patients who required a change in antiepileptic drug (AED) regimen and substituted at least one AED with brivaracetam.

Methods: In this retrospective noninterventional study conducted in specialized epilepsy centers across Germany, patients initiated adjunctive brivaracetam between February 15, 2016, and August 31, 2016, as part of an intended change in AED regimen. The primary effectiveness variable was the proportion of patients who continued on brivaracetam after 3 months, and withdrew at least one AED either before or within 6 months after brivaracetam initiation.

Results: Five hundred and six patients had at least one brivaracetam dose and were included in the safety set (SS). Four hundred and seventy patients started to reduce the dose of one AED before/after brivaracetam initiation, had at least one concomitant AED at brivaracetam initiation, and were included in the full analysis set (FAS) for effectiveness analyses. At baseline, patients had a median of seven lifetime AEDs and a median of 3.8 seizures/28 days. In the SS, 85.2% of patients withdrew one AED before/after initiation of brivaracetam, most commonly levetiracetam (49.4%). 46.2% of patients substituted another AED with brivaracetam within 24 hours (fast withdrawal). The proportions of patients (FAS) who continued on brivaracetam after 3 and 6 months and withdrew one AED were 75.5% and 46.6%, respectively. After 6 months, 32.1% of patients were 50% responders; 13.0% were seizure-free. In the SS, 34.6% of patients reported treatment-emergent adverse events (TEAEs); 21.9% had TEAEs that were assessed by the treating physician as drug-related. Incidences of behavioral AEs before (3-month baseline) and after brivaracetam initiation in patients who withdrew levetiracetam were 19.2% and 8.0%, respectively (5.0% and 7.7% in patients who withdrew other AEDs).

Significance: Brivaracetam was effective and well-tolerated in patients who required a change in AED drug regimen and initiated adjunctive brivaracetam in German clinical practice.

KEYWORDS

antiseizure; behavioral adverse events, drug-resistant epilepsy, focal seizures, noninterventional

1 | INTRODUCTION

Brivaracetam is an antiepileptic drug (AED) with highly selective affinity for the synaptic vesicle protein 2A (SV2A).[1] Brivaracetam is approved for adjunctive therapy of focal (partial-onset) seizures in patients ≥4 years of age in the European Union, and as monotherapy and adjunctive therapy in patients ≥4 years of age in the United States.[2,3] A pooled analysis of three randomized, double-blind, placebo-controlled trials showed that brivaracetam was effective in adults with focal seizures and was generally well-tolerated across the therapeutic dose range.[4] Reduction over placebo in baseline-adjusted focal seizure frequency/28 days was 19.5% for 50 mg/d brivaracetam ($P = .0015$), 24.4% for 100 mg/d ($P < .00001$), and 24.0% for 200 mg/d ($P < .00001$). Treatment-emergent adverse events (TEAEs) reported in ≥5% of patients taking brivaracetam (vs placebo) were somnolence (15.2% vs 8.5%), dizziness (11.2% vs 7.2%), and fatigue (8.7% vs 3.7%).

Data from observational studies help to bridge the gaps between registration data and the data needed for physicians in order to most effectively utilize a new treatment in clinical practice. The main objective of this multicenter, noninterventional, retrospective study conducted in specialized epilepsy centers across Germany was to evaluate the success of initiation of brivaracetam as adjunctive therapy in patients who required a change in their existing drug regimen and substituted at least one of their AEDs with brivaracetam. Subgroup analyses were performed to investigate brivaracetam effectiveness by the speed of withdrawal of the substituted AED. In addition, the safety and tolerability profile of brivaracetam in clinical practice was observed, with a focus on behavioral TEAEs. Tolerability data were analyzed for the overall population and for subgroups of patients who withdrew levetiracetam and who withdrew other AEDs. Data for patients who withdrew levetiracetam upon brivaracetam initiation are of particular interest, as both AEDs are SV2A ligands; however, brivaracetam shows a more specific SV2A receptor interaction than levetiracetam, which may be associated with an improved safety profile.[5]

Key Points

- Retrospective study evaluated success of initiation of adjunctive brivaracetam in patients who required a change in AED regimen.
- Levetiracetam was the most commonly withdrawn AED upon brivaracetam initiation, most patients substituted levetiracetam within 24 hours.
- Most patients (75.5%) continued on brivaracetam 3 months after initiation and had total withdrawal of at least one AED.
- Given the drug-resistant patient population, the observed 50% responder (32.1%) and seizure-freedom rates (13.0%) after 6 months were high.
- In patients who withdrew levetiracetam, the incidence of behavioral AEs was lower following brivaracetam initiation (19.2% vs 8.0%).

2 | METHODS

EP0104 was a multicenter, retrospective, noninterventional chart review conducted at 20 specialized epilepsy centers in Germany. At each participating site, brivaracetam-treated patients with epilepsy who were eligible for data collection according to the selection criteria were identified by review of their medical records. Eligible patients had a confirmed diagnosis of epilepsy and initiated brivaracetam as adjunctive therapy between February 15, 2016, and August 31, 2016, as part of an intended change in their existing AED regimen. Additional patient selection criteria were the start of dose reduction in an AED other than brivaracetam either before or within 1 month after brivaracetam initiation. Three observation points were defined for data collection: the patient's first day of treatment with brivaracetam (OP1), and ~3 months (OP2) and ~6 months (OP3; up to 225 days after initiation) thereafter.

The primary effectiveness variable was the proportion of patients who continued on brivaracetam 3 months after initiation and withdrew at least one AED, either before brivaracetam initiation or during the 6 months after brivaracetam initiation. Secondary effectiveness variables were the proportion of patients who continued on brivaracetam 6 months after initiation and withdrew at least one AED, and the incidence and time to discontinuation of brivaracetam treatment (due to the occurrence of a TEAE, due to lack of effectiveness, and in patients with a reduction in seizure frequency of <50% as compared with baseline). Other effectiveness variables were the change in seizure frequency/28 days from baseline to 6 months after brivaracetam initiation, and 50% and 100% responder (seizure-freedom) rates (patients with a ≥50% and 100% reduction in seizure frequency/28 days). The speed of withdrawal of the AED substituted with brivaracetam (time for total withdrawal of another AED) was also assessed, and subgroup analyses were performed. Safety and tolerability variables were the incidence of prior adverse events (AED-related AEs with onset before brivaracetam initiation), and the incidence and seriousness of TEAEs (AEs with onset on/after the date of first brivaracetam dose and no later than 30 days after the last dose), including behavioral TEAEs, observed during the 6-month observational period. Behavioral AEs were defined as any event with a Medical Dictionary for Regulatory Activities (MedDRA) preferred term listed in Appendix 1.

2.1 | Statistical analyses

Safety/tolerability analyses were performed using the safety set (SS), which included all patients who had at least one brivaracetam administration. Effectiveness analyses were performed using the full analysis set (FAS), which included all SS patients who started the dose reduction in at least one AED before or after brivaracetam initiation, and who had at least one concomitant AED at brivaracetam initiation. Effectiveness analyses were also performed for the modified FAS (mFAS), a subset of the FAS which included all patients who started the dose reduction in at least one AED within 3 months before or 1 month after brivaracetam initiation, and used brivaracetam according to the European Summary of Product Characteristics (SmPC).[2]

A formal statistical sample size determination was not performed, as only exploratory statistics were planned. As a sensitivity analysis, time to discontinuation of brivaracetam treatment was analyzed using the Kaplan-Meier methods. The Kaplan-Meier-estimated retention rates were calculated for both the FAS and mFAS (irrespective of whether an AED had been totally withdrawn or not) and by speed of withdrawal subgroups. Subgroup analyses of retention and responder rates were performed for patients with fast withdrawal of the substituted AED (within 24 hours either before/after brivaracetam initiation), medium withdrawal (within >24 hours to 4 weeks [1 month]) after brivaracetam initiation, and slow withdrawal (within >4 to 24 weeks [1-6 months]) after brivaracetam initiation. Safety and tolerability data were also analyzed for patient subgroups by levetiracetam withdrawal and any other AED withdrawal. Statistical analyses were conducted using SAS Version 9.4.

3 | RESULTS

3.1 | Patients

A total of 507 patients were documented at 20 sites, of whom 506 had at least one dose of brivaracetam and were included in the SS (Figure S1). The FAS included 470 patients who started the dose reduction in one AED before or after brivaracetam initiation and had one concomitant AED. Out of these 470 patients, 253 patients were included in the mFAS. The most common reason for exclusion from the mFAS was treatment with brivaracetam outside of the recommended European SmPC (eg, daily dose <50 or >200 mg; administration not twice daily in equally divided dose; monotherapy; age at baseline <16 years old, nonfocal seizures).

Overall, 332 of 507 (65.5%) enrolled patients continued on brivaracetam after 6 months (225 days after initiation; OP3). One hundred and twenty-nine (25.4%) patients discontinued brivaracetam (due to lack of efficacy: 63 [12.4%]; other intolerance: 26 [5.1%]; behavioral side effects: 22 [4.3%]; missing reason: 11 [2.2%]; other reason: 7 [1.4%]), and 1 (0.2%) patient was lost to follow-up.

Patients in the SS had a mean (SD) age of 41.6 (15.9) years, and 52.4% were male. Most (89.9%) were aged between 18 and <65 years. The most common reasons for initiation of brivaracetam were lack of effectiveness of current AED treatment (333 [65.8%] patients) and behavioral side effects of current AED treatment (101 [20.0%]). Patients had a median of 3.8 seizures/28 days during the 3-month historical baseline period (Table 1) and median of 7 (range: 1-44) lifetime AEDs, 327 (64.6%) had prior treatment with levetiracetam, and 143 (28.2%) used levetiracetam concomitantly during the observational period. Patient characteristics were similar in the mFAS (Table S1).

3.2 | Brivaracetam exposure and AED withdrawal

In the SS, the mean (SD) brivaracetam treatment duration was 170.5 (81.2) days (median: 182.0 [range: 1-574] days). Treatment duration was similar in subgroups of patients who withdrew levetiracetam (mean [SD]: 175.5 [79.0] days; n = 249) and who withdrew any other AED (175.6 [81.7] days; n = 179). The median initiation dose of brivaracetam was 100 mg/d (range: 10-400 mg/d). A modal dose of 200 mg/d was taken by 214/427 (50.1%) patients between baseline and 3 months, and 149/280 (53.2%) patients between 3 and 6 months (Table 2). At the 6-month observation, the median brivaracetam dose was 200 mg/d (range: 50, 400 mg/d). Doses were similar in the mFAS (Table S2).

Most patients (431 [85.2%]) had a substitution with brivaracetam and withdrew at least one AED either before or after initiation of brivaracetam. The most commonly withdrawn AED was levetiracetam (250 [49.4%]), followed by lacosamide (47 [9.3%]) and valproic acid (42 [8.3%]) (Table 2). Overall, 234 (46.2%) patients withdrew an AED within 24 hours either before/after brivaracetam initiation (fast withdrawal). The most commonly withdrawn AEDs (>15% of patients in the respective subgroup) were levetiracetam (184/234 [78.6%]) in the fast withdrawal subgroup; levetiracetam (34/127 [26.8%]) and lacosamide (25/127 [19.7%]) in the medium withdrawal subgroup (within >24 hours to 1 month after brivaracetam initiation); and levetiracetam (11/31 [35.5%]), oxcarbazepine (6/31 [19.4%]), and lacosamide (5/31 [16.1%]) in the slow withdrawal subgroup (within >1 up to 6 months after brivaracetam initiation).

3.3 | Effectiveness

The proportions of patients in the FAS who continued on brivaracetam 3 and 6 months after initiation and had total

TABLE 1 Baseline characteristics and concomitant AEDs

	SS[a] (N = 506)
Epilepsy history	
Duration of epilepsy, mean (SD), y	24.9 (16.1)[b]
Baseline seizure frequency/28 d, median (Q1, Q3)[c]	
All seizures	3.8 (0.9, 14.9)[d]
Focal seizures	4.4 (1.5, 18.1)[e]
Focal seizures with secondary generalization	0.0 (0.0, 0.7)[f]
Concomitant AEDs, n (%)[g]	
Concomitant AEDs taken by ≥15% of patients	
Lamotrigine	216 (42.7)
Lacosamide	161 (31.8)
Levetiracetam	143 (28.3)
Valproic acid	141 (27.9)
Zonisamide	79 (15.6)
Concomitant AED combinations taken by ≥5% of patients	
Lamotrigine/valproic acid	54 (10.7)
Lamotrigine/lacosamide	27 (5.3)
Levetiracetam/lacosamide	27 (5.3)
Levetiracetam/lamotrigine	26 (5.1)
Medical history conditions, n (%)	
Any previous/ongoing medical conditions	506 (100)
Previous/ongoing medical conditions in ≥5% of patients	
Depression	54 (10.7)
Hypertension	31 (6.1)

Abbreviations: AED, antiepileptic drug; Q1, first quartile; Q3, third quartile; SD, standard deviation; SS, safety set.

[a]Baseline characteristics were similar for the safety set and full analysis set, given the similar patient numbers (safety set: 506; full analysis set: 470).

[b]n = 505.

[c]Based on historical baseline.

[d]n = 461.

[e]n = 390.

[f]n = 384.

[g]Any AED that started before the first dose of brivaracetam treatment and continued to be taken after the first dose of brivaracetam treatment, or any AED that started at the time of or after the first dose of BRV treatment, but not after the last dose of BRV treatment.

TABLE 2 Brivaracetam dosing and AEDs withdrawn

	SS (N = 506)	
	Baseline to 3 mo (N = 427)[b]	**3-6 mo (N = 280)[c]**
Modal brivaracetam dose, n (%)[a]		
20 mg/d	1 (0.2)	1 (0.4)
50 mg/d	26 (6.1)	24 (8.6)
100 mg/d	144 (33.7)	80 (28.6)
150 mg/d	42 (9.8)	26 (9.3)
200 mg/d	214 (50.1)	149 (53.2)
Speed of AED withdrawal[d,e]		
Fast (within 24 h)	234 (46.2)	
Medium (within 1 mo)	127 (25.1)	
Slow (within >1 to 6 mo)	31 (6.1)	
Other	32 (6.3)	
Missing	82 (16.2)	
AEDs withdrawn by ≥4% of patients before/after initiation of brivaracetam, n (%)[f]		
Levetiracetam	250 (49.4)	
Lacosamide	47 (9.3)	
Valproic acid	42 (8.3)	
Zonisamide	31 (6.1)	
Clobazam	28 (5.5)	
Topiramate	28 (5.5)	
Oxcarbazepine	27 (5.3)	
Perampanel	27 (5.3)	
Lamotrigine	24 (4.7)	

Abbreviations: AED, antiepileptic drug; SD, standard deviation; SS, safety set.

[a]The modal dose is the dose that was taken most often by the individual patient within the specified time period.

[b]Baseline to 3 mo = days 1-90.

[c]3-6 mo = days 91-180.

[d]If the patient withdrew multiple AEDs, only the fastest speed was considered.

[e]Fast = within 24 h before or after brivaracetam initiation; medium >24 h to 28 d; slow >28 d to 168 d; other = >168 d or up to 3 mo (>24 h and ≤90 d) before brivaracetam initiation.

[f]Multiple AEDs could be withdrawn per patient.

withdrawal of one AED were 75.5% and 46.6%, respectively (Figure 1A). Irrespective of whether an AED had been totally withdrawn or not, the Kaplan-Meier-estimated 6-month retention on brivaracetam was 70.7% (Figure 1B; Table S3). As assessed by the treating physician, the occurrence of a TEAE was the main reason for discontinuation of brivaracetam in 48 (10.2%) patients, and lack of efficacy was the main reason for discontinuation of brivaracetam in 60 (12.8%) patients. The Kaplan-Meier-estimated 6-month retention rates were similar when the main reason for brivaracetam discontinuation (assessed by the treating physician) was occurrence of a TEAE (91.5%) or lack of efficacy (87.8%). A total of 233 patients had a <50% seizure reduction, of whom 82 (35.2%) discontinued brivaracetam due to any reason. In this subgroup, the Kaplan-Meier-estimated 6-month retention rate was 70.1%. Overall, the median percent change from historical baseline in seizure frequency/28 days after 6 months was −36.4%; 32.1% of patients were 50% responders, and 13.0% were seizure-free (Figure 1C). Similar effectiveness results were observed in

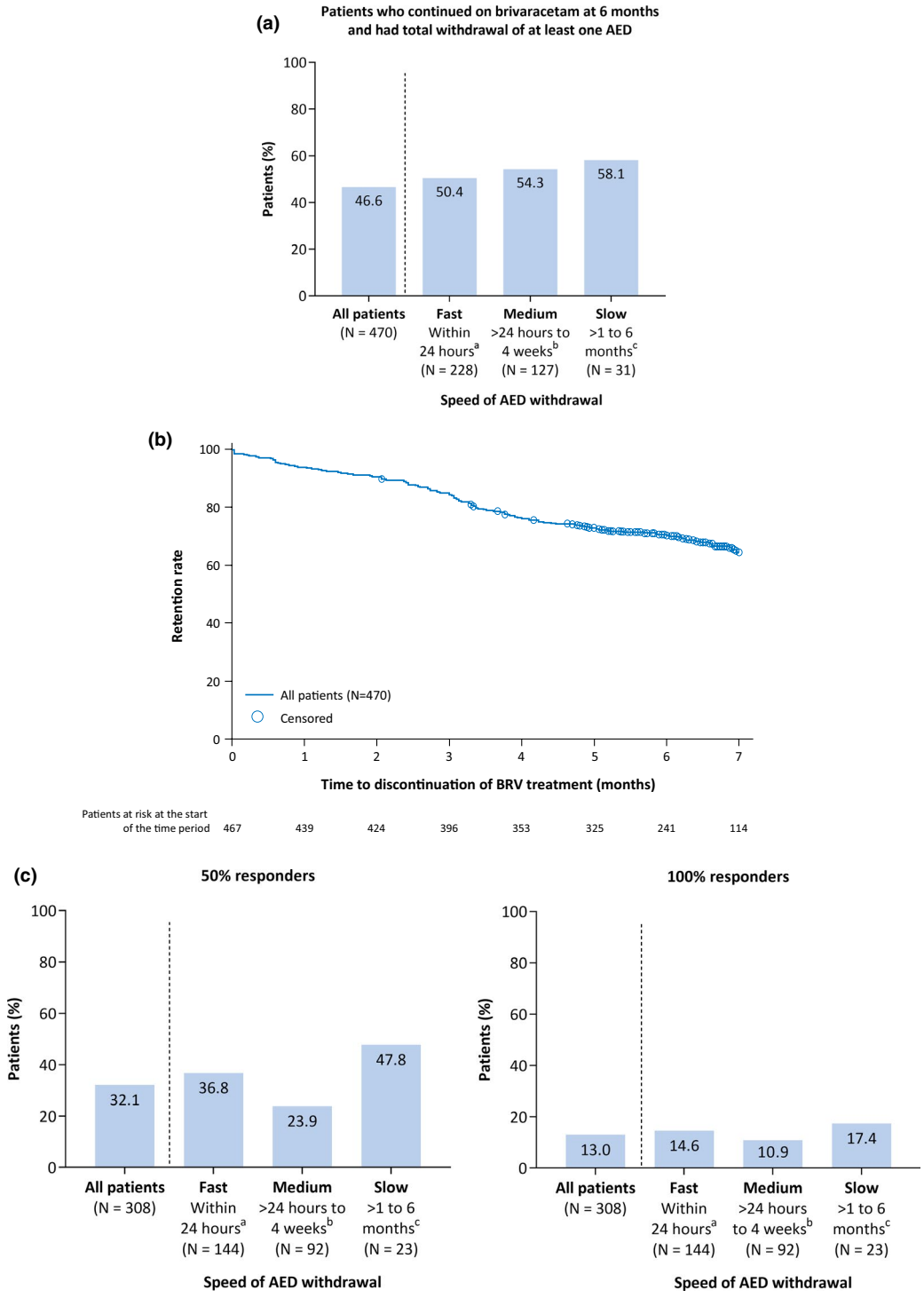

FIGURE 1 A, Retention on brivaracetam at 6 mo, for all patients and for subgroups of patients with fast, medium, and slow withdrawal of the substituted AED (FAS). B, Kaplan-Meier plot for time to discontinuation of brivaracetam (FAS). C, Responder rates at 6 mo for all patients and for subgroups of patients with fast, medium, and slow withdrawal of the substituted AED (FAS). [a]Total withdrawal within a maximum of 24 h before or after brivaracetam initiation; [b]Total withdrawal within >24 h to 4 wk after brivaracetam initiation; [c]Total withdrawal within >4 to 24 wk after brivaracetam initiation. N numbers below each bar represent the total number of patients in each subgroup. FAS, full analysis set

patients treated as recommended by the European SmPC (mFAS; Figure S2, Table S3; Figure S3).

Subgroup analyses by speed of substituted AED withdrawal (FAS) showed 50.4% of patients in the fast withdrawal subgroup, 54.3% in the medium withdrawal subgroup, and 58.1% in the slow withdrawal subgroup continued on brivaracetam 6 months after initiation (Figure 1A). Numerically higher 50% responder rates were observed in patients with slow withdrawal of the substituted AED compared with those with fast or medium AED withdrawal (Figure 1C). Seizure

freedom was reported for 14.6% of patients in the fast AED withdrawal subgroup, 10.9% in the medium AED withdrawal subgroup, and 17.4% in the slow AED withdrawal subgroup.

3.4 | Safety and tolerability

Of all treated patients (SS), 175 (34.6%) reported TEAEs during brivaracetam treatment and 111 (21.9%) had drug-related TEAEs as assessed by the treating physicians (Table 3). Most patients had TEAEs of mild or moderate intensity. The most commonly reported TEAEs by system organ class (≥10% of patients) were nervous system disorders (76 [15.0%]) and psychiatric disorders (67 [13.2%]). TEAEs leading to discontinuation of brivaracetam in ≥1% of patients were aggression (13 [2.6%]), seizure (10 [2.0%]), dizziness (5 [1.0%]), and fatigue (5 [1.0%]). No deaths were reported during observation of up to 6 months.

During the 3-month baseline, 158 (31.2%) patients reported prior AEs before brivaracetam treatment, most commonly (≥3% of patients) aggression, depression, fatigue, and irritability (Table 4). Following the initiation of brivaracetam, 141 (27.9%) patients had TEAEs within the first 3 months, and 30 (5.9%) had TEAEs during the last 3 months of the observational period (Table 4). Aggression, depression, fatigue, and irritability were each reported in <1% of patients during the last 3 months of observation.

TABLE 3 Incidence of TEAEs (including behavioral) during the observational period (SS)

	All patients (N = 506)	Levetiracetam withdrawn (N = 250)	Other AED withdrawn (N = 181)
Any TEAEs, n (%)	175 (34.6)	79 (31.6)	72 (39.8)
Serious TEAE	29 (5.7)	11 (4.4)	14 (7.7)
Discontinuation due to TEAEs	66 (13.0)	27 (10.8)	25 (13.8)
Drug-related TEAEs	111 (21.9)	47 (18.8)	44 (24.3)
Severe TEAEs	23 (4.5)	8 (3.2)	13 (7.2)
TEAEs leading to death	0	0	0
Most common TEAEs (≥1% of all patients)[a]			
Fatigue	26 (5.1)	11 (4.4)	12 (6.6)
Seizure[b]	24 (4.7)	12 (4.8)	9 (5.0)
Dizziness	16 (3.2)	9 (3.6)	4 (2.2)
Depression	7 (1.4)	3 (1.2)	3 (1.7)
Somnolence	7 (1.4)	2 (0.8)	2 (1.1)
Gait disturbance	6 (1.2)	3 (1.2)	3 (1.7)
Alopecia	5 (1.0)	3 (1.2)	2 (1.1)
Ataxia	5 (1.0)	2 (0.8)	2 (1.1)
Insomnia	5 (1.0)	1 (0.4)	3 (1.7)
Mood altered	5 (1.0)	3 (1.2)	2 (1.1)
Nausea	5 (1.0)	1 (0.4)	4 (2.2)
Status epilepticus	5 (1.0)	1 (0.4)	2 (1.1)
Vertigo	5 (1.0)	3 (1.2)	1 (0.6)
Any behavioral AE/TEAE, n (%)	39 (7.7)	20 (8.0)	14 (7.7)
Most common behavioral AEs/TEAEs (≥1% of all patients)[a]			
Aggression	24 (4.7)	11 (4.4)	11 (6.1)
Irritability	11 (2.2)	7 (2.8)	3 (1.7)

Abbreviations: ADR, adverse drug reaction; AE, adverse event; AED, antiepileptic drug; SS, safety set; TEAE, treatment-emergent adverse event.

[a]Preferred term.

[b]Seizures were recorded as AEs/TEAEs if their nature changed considerably or their frequency/intensity increased in a clinically significant manner as compared with the clinical profile known to the treating physician from the patient's history or the baseline period.

The incidences of TEAEs and drug-related TEAEs were numerically lower in patients who withdrew levetiracetam (N = 250) compared with those who withdrew other AEDs (N = 181) (Table 3). In patients who withdrew levetiracetam, behavioral AEs were reported by 48 (19.2%) patients during 3-month baseline and 20 (8.0%) patients following initiation of brivaracetam. In patients who withdrew other AEDs, behavioral AEs were reported by 9 (5.0%) patients during baseline and 14 (7.7%) patients following initiation of brivaracetam.

Aggression and irritability were the most common behavioral TEAEs during the observational period (Table 3). In patients who withdrew levetiracetam, aggression was reported by 29 (11.6%) patients during 3-month baseline and by 3 (1.2%) patients during the last 3 months of observation; irritability was reported by 12 (4.8%) patients during baseline and by 1 (0.4%) patient during months 3-6. In patients who withdrew other AEDs, aggression was reported by 6 (3.3%) patients during baseline and 1 (0.6%) patient during the last 3 months of observation; 3 (1.7%) patients reported irritability during baseline and none during months 3-6.

TABLE 4 Prior AEs/TEAEs (including behavioral) by time of occurrence (SS; N = 506)

	3-mo baseline	Observational period	
	Prior AEs	Baseline to 3 mo	3-6 mo
Any AE/TEAEs, n (%)	158 (31.2)	141 (27.9)	30 (5.9)
Most common AEs/TEAEs (≥2% of patients in any time period) before or during brivaracetam treatment[a]			
Fatigue	17 (3.4)	24 (4.7)	2 (0.4)
Seizure[b]	3 (0.6)	16 (3.2)	5 (1.0)
Dizziness	10 (2.0)	13 (2.6)	2 (0.4)
Depression	23 (4.5)	4 (0.8)	2 (0.4)
Any behavioral AE/TEAE, n (%)	63 (12.5)	33 (6.5)	5 (1.0)
Most common behavioral AEs/TEAEs (≥2% of patients in any time period) before or during brivaracetam treatment[a]			
Aggression	38 (7.5)	20 (4.0)	4 (0.8)
Irritability	16 (3.2)	9 (1.8)	1 (0.2)

Note: The historical baseline is the 3-mo period before brivaracetam initiation. Baseline to 3 mo = days 1-90, 3-6 mo = days 91-180.

Abbreviations: AE, adverse event; SS, safety set; TEAE, treatment-emergent adverse event.

[a]Preferred term.

[b]Seizures were recorded as AEs/TEAEs if their nature changed considerably or their frequency/intensity increased in a clinically significant manner as compared with the clinical profile known to the treating physician from the patient's history or the baseline period.

4 | DISCUSSION

This retrospective noninterventional study collected data on patients who initiated adjunctive brivaracetam according to physicians' decisions in a real-world setting. Brivaracetam was prescribed to patients with treatment-resistant epilepsy, as shown by their high number of lifetime AEDs (median: 7.0) and high seizure frequency (median: 3.8 seizures/28 days). Most patients (65.8%) initiated brivaracetam due to lack of effectiveness of their current treatment. In most cases (91.7%), brivaracetam was initiated at a therapeutic dose (50-200 mg/d). 50.1% of patients had a modal dose of 200 mg/d between baseline and 3 months, and 53.2% had a modal dose of 200 mg/d between 3 and 6 months.

The majority of patients (FAS: 75.5%) remained on brivaracetam after 3 months and withdrew one AED either before or during the 6-month observation. The proportion of patients who remained on brivaracetam after 6 months and substituted one concomitant AED with brivaracetam was 46.6%. Irrespective of whether an AED had been totally withdrawn or not, the Kaplan-Meier-estimated 6-month retention with censoring of patients without documented discontinuation of brivaracetam was 70.7%. Retrospective studies of brivaracetam have reported 6-month retention rates of 51.5-80.2%.[6–9] A Kaplan-Meier-estimated 6-month retention rate of 91.0% was reported in a pooled analysis of data from 2051 patients with uncontrolled focal seizures treated with adjunctive brivaracetam (modal doses of 50-200 mg/d) in randomized controlled trials and long-term follow-up studies.[10]

The median percent change from historical baseline in seizure frequency/28 days was −36.4% after 6 months; 32.1% of patients (FAS) were 50% responders, and 13.0% were seizure-free. Other retrospective studies have reported 50% responder rates of 27.8%-40.5% and seizure-freedom rates of 7.0%-21.7% after 6 months of brivaracetam treatment.[6–9] Pooled data from long-term follow-up studies of adjunctive brivaracetam showed that 50.6% of patients had a 50% reduction in focal seizure/frequency/28 days after 6 months, with 4.9% remaining seizure-free.[10]

Effectiveness variables were evaluated separately for all patients in the FAS, and for patients who were treated according to the recommendations of the European SmPC and started to change the dose of one other AED within 3 months before or 1 month after brivaracetam initiation (mFAS). Reasons for exclusion from the mFAS were daily dose <50 or >200 mg; administration not twice daily in equally divided dose; monotherapy; age at baseline <16 years; and nonfocal seizures. Effectiveness analyses on the FAS and mFAS did not show any meaningful differences.

Substitution of an existing AED with brivaracetam was conducted at the physician's discretion. Fast AED withdrawal (within 24 hours before/after brivaracetam initiation) was the most common approach (46.2% of patients), with few

patients continuing on the AED intended for withdrawal after 1 month of brivaracetam treatment. Levetiracetam was the AED most commonly withdrawn upon initiation of brivaracetam, and most patients who withdrew levetiracetam did so within 24 hours. Observational studies have shown that an immediate substitution of levetiracetam with brivaracetam is well-tolerated, with no increased risk of seizures.[6,8,11] In a German multicenter retrospective study, 78.9% of patients switched from levetiracetam to brivaracetam within a median time period of 1 day.[8]

Subgroup analyses showed 6-month retention on brivaracetam with total withdrawal of one AED ranged from 50.4% to 58.1% in patients with fast (within 24 hours), medium (within 1 month), and slow (within >1 to 6 months) withdrawal of the substituted AED. Seizure reduction assessments (50% and 100% responder rates) indicated that BRV was generally effective regardless of the speed of AED withdrawal. These analyses should be interpreted with caution, as few patients had slow withdrawal of the substituted AED (n = 31) and the AEDs withdrawn differed between the subgroups. Levetiracetam was withdrawn by 78.6% of patients in the fast withdrawal subgroup, 26.8% in the medium withdrawal subgroup, and 35.5% in the slow withdrawal subgroup.

Adjunctive brivaracetam was generally well-tolerated, with a safety profile similar to that observed in clinical studies.[10] The incidence of TEAEs during the first 3 months following brivaracetam initiation (27.9%) was similar to the incidence of prior AEs observed during the 3-month historical baseline (31.2%). Few patients (5.9%) reported TEAEs during months 3-6. The incidence of drug-related TEAEs was similar among patients who withdrew levetiracetam (18.8%) and those who withdrew other AEDs (24.3%), indicating that brivaracetam was well-tolerated regardless of the AED substituted with brivaracetam.

Although the efficacy and tolerability of levetiracetam for patients with epilepsy have been established in numerous randomized, double-blind, controlled trials,[12–14] it has been associated with behavioral TEAEs such as irritability and aggression.[15] In the current noninterventional study, behavioral side effects with their current AEDs were reported as the main reason for initiating brivaracetam treatment in 20% of patients. In patients who withdrew levetiracetam, a lower incidence of behavioral AEs was observed following BRV initiation (19.2% vs 8.0%), whereas in patients who withdrew other AEDs the incidence of behavioral AEs was similar before and after BRV initiation (5.0% vs 7.7%). The lower incidence of behavioral AEs observed following the initiation of brivaracetam in patients who withdrew levetiracetam is consistent with the results of previous studies. In an open-label prospective study, 93.1% (27/29) of patients who switched directly from levetiracetam to brivaracetam without titration (n = 29) had clinically meaningful reductions in behavioral AEs.[5] A retrospective multicenter cohort study showed that switching to brivaracetam alleviated levetiracetam-induced behavioral AEs in 57% (20/35) of patients.[8] Similarly, a retrospective single-center study showed a relevant improvement in 57% (28/49) of patients who had switched from levetiracetam to brivaracetam because of psychiatric side effects.[6] Another retrospective study conducted at a single epilepsy center showed that 77.2% (44/57) of patients who had experienced AEs during levetiracetam treatment (either at study baseline, or in their prior medical history) had a clinically meaningful reduction or no re-emergence of previous levetiracetam-related AEs with brivaracetam.[11]

5 | CONCLUSION

The results of this retrospective study in patients who required a change in their existing drug regimen and initiated brivaracetam as adjunctive therapy indicate that brivaracetam was effective and well-tolerated in German clinical practice. In patients who withdrew levetiracetam, a lower incidence of behavioral side effects was observed following initiation of brivaracetam. The main limitations are the retrospective nature of the study with analyses based on chart reviews (missing data may lead to difficulties in assessment of secondary variables) and the relatively short observation of up to 6 months.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Iryna Leunikava participated in the development of the concept and design of the study, on behalf of UCB Pharma. Holger Lerche contributed to the conception and design of the study, and was the coordinating physician. Anne-Liv Schulz was the study physician. Holger Lerche, Susanne Knake, Felix Rosenow, and Peter Hopp participated in acquisition of data as study investigators. Scarlett Hellot was the study statistician. All authors participated in analysis and interpretation of results and critical revision of the article for intellectual content. All authors approved the final version of the manuscript for publication.

DATA AVAILABILITY STATEMENT

Data from noninterventional studies are outside of UCB Pharma's data sharing policy and are unavailable for sharing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX 1

Antiepileptic drug-related behavioral adverse events and behavioral treatment-emergent adverse events were defined as any events with the following MedDRA 18.1 preferred terms:

Aggression	Disturbance in social behaviour
Amygdalotomy	Drowning
Anger	Elder abuse
Antisocial behaviour	Fight in school
Antisocial personality disorder	Gunshot wound
Belligerence	Human bite
Borderline personality disorder	Hypomania
Child abuse	Impatience
Conduct disorder	Imprisonment
Homicidal ideation	Imprisonment of relative
Homicide	Impulse-control disorder
Hostility	Impulsive behaviour
Incest	Injury
Intermittent explosive disorder	Irritability
Physical abuse	Jealous delusion
Physical assault	Laceration
Psychopathic personality	Mania
Sexual abuse	Oppositional defiant disorder
Violence-related symptom	Paedophilia
Abnormal behaviour	Paranoia
Activation syndrome	Paranoid personality disorder
Affect lability	Paraphilia
Agitated depression	Personality change
Agitation	Personality disorder
Agitation postoperative	Psychological abuse
Asphyxia	Psychomotor hyperactivity
Attention-seeking behaviour	Psychotic behaviour
Bipolar disorder	Psychotic disorder
Bipolar I disorder	Pyromania
Bipolar II disorder	Sadism
Bite	Schizophrenia, paranoid type
Delinquency	Screaming
Delusional disorder, jealous type	Spousal abuse
Delusional disorder, persecutory type	Stab wound
Disinhibition	Substance-induced psychotic disorder
Theft	Verbal abuse

CO-INVESTIGATOR APPENDIX

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