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Adjunctive brivaracetam in focal and generalized epilepsies: A single-center open-label prospective study in patients with psychiatric comorbidities and intellectual disability

Eng Chuan Foo *, Jo Geldard, Caroline Peacey, Elizabeth Wright, Khalid Eltayeb, Melissa Maguire

Department of Neurology, Leeds Teaching Hospitals, Leeds, United Kingdom

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ABSTRACT

Clinical studies suggest that the antiepileptic drug (AED) brivaracetam (BRV) is associated with fewer behavioral and psychiatric adverse events (AEs) compared with levetiracetam (LEV) in treating epilepsy. There are, however, few comparative studies of treatment-emergent AEs between patients on BRV with preexisting psychiatric or behavioral comorbidities to those without. Our study compared longer-term tolerability over a 26-month period between these patient groups and assessed the overall efficacy of BRV as add-on therapy. Patients with intellectual disabilities in whom the prevalence of epilepsy is higher, are often excluded from randomized controlled trials, and our study further assessed comparative effectiveness between this patient group and those with normal range intellect.

We collected prospective data on 134 patients prescribed add-on BRV for epilepsy at a tertiary UK center over a 26-month period. All patients had previously received LEV. Sixty-three patients were on LEV at the start of the data collection period. Levetiracetam was withdrawn and switched to BRV in 39 patients because of inefficacy and 24 patients because of behavioral or psychiatric side effects.

Seventy-three patients (54%) had a preexisting psychiatric or behavioral disorder compared with 64 patients (46%) without. The retention rate at last follow-up [mean: 11 months (0.5–26 months)] was 60% in the psychiatric/behavioral disorders group versus 67% in those without ($p = 0.68$). Forty-one patients had diagnosed intellectual disabilities. The retention rate was 66% in this group versus 62% in patients without intellectual disabilities ($p = 0.36$). The commonest treatment-emergent AEs were somnolence (26%), aggression (23%), and depression (9%). There were similar frequencies reported for these specific events across the groups.

The proportion with a 50% responder rate was 29% in patients with focal epilepsy and 47% in patients with generalized and combined focal and generalized epilepsies. However, fifteen patients (11%) reported increased seizure activity leading to withdrawal of treatment.

This study showed evidence that BRV may be an effective adjunctive therapy in patients with drug-resistant focal or generalized epilepsies whose seizures have previously not responded or tolerated LEV therapy. We demonstrated a higher incidence of treatment-emergent AEs leading to lower retention rates compared with previous studies across all patient groups. There were, however, no significant differences in tolerability between patients with preexisting psychiatric or behavioral comorbidities, or intellectual disability to those without.

1. Introduction

Brivaracetam (BRV) is licensed in the European Union as an adjunctive antiepileptic drug (AED) for treatment of focal epilepsy in adults. It is a selective, high-affinity ligand with 15- to 30-fold higher affinity than levetiracetam (LEV) to synaptic vesicle protein 2A (SV2A) [1].

Levetiracetam is associated with psychiatric and behavioral adverse events (AEs), including aggression and depression [2]. Clinical studies have suggested that BRV is associated with less behavioral and psychiatric AEs compared with LEV [3–6]. Safety and tolerability studies have reported that the most common treatment-emergent AEs are headaches (20.9%), dizziness (17.5%), and somnolence (15.2%) with the incidence of aggression or irritability as an AE reported as low (5.2%) [7]. A recent meta-analysis of randomized controlled trials assessing the AE profile of BRV reported no significant increase of psychiatric AEs in patients on BRV across all dosages versus placebo. This review also reported a good tolerability profile for BRV with no significant difference to placebo. The primary cause leading to withdrawal of treatment was psychiatric AEs

Abbreviations: AED, antiepileptic drug; AE, adverse event; LEV, levetiracetam; BRV, brivaracetam.

* Corresponding author at: Neurology Department, Martin Wing G Floor, Leeds General Infirmary, Leeds, LS1 3EX, United Kingdom.
E-mail address: engchuan.foo@nhs.net (E.C. Foo).

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and lack of treatment efficacy [8]. These studies, however, did not assess and compare the AEs between patients with preexisting psychiatric and behavioral comorbidities with those without.

There is a higher prevalence of epilepsy in patients with intellectual disability compared with the general population [9]. This appears to be an insufficiently studied aspect, and to date, there has been a single retrospective study of tolerability and AE profile in patients with intellectual disability. This was, however, conducted in a small patient population size of 33 patients [10].

The objectives of our prospective study were to assess overall efficacy, tolerability, retention rate, and longer-term AE profile of BRV in patients with preexisting psychiatric or behavioral comorbidities to those without. We also aimed to identify any differences in patients with intellectual disability compared with those with normal range intellect.

2. Methods

2.1. Study design & participants

This was a prospective observational study investigating the efficacy and tolerability of BRV (25 mg–200 mg/day) as adjunctive therapy in drug-resistant epilepsy. Drug-resistant epilepsy was defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [11]. Brivaracetam was prescribed for adult patients (≥16 years old) with focal or generalized epilepsy with or without intellectual disability and/or psychiatric comorbidities. Patients were recruited from one UK site (Leeds Teaching Hospitals NHS Trust epilepsy service) and prospectively followed up at clinic appointments over a 26-month period (May 2016 to July 2018).

2.2. Assessment methods

Baseline characteristics of participants (age, sex, epilepsy type, epilepsy duration, number or previously tried AEDs, number of concomitant AEDs, history of psychiatric or behavioral issues, preexisting diagnosis of intellectual disability, and LEV status [tried or untried]) were obtained from hospital clinic correspondence, hospital electronic records, and general practitioner (GP) records.

Efficacy was assessed from a patient-recorded seizure diary at each visit, where seizure types could be classified along with calculated frequencies of seizures. Adverse events were documented during each clinic visit to establish any association with BRV or potential interactions with concomitant medications. Patients were then reassessed either through a telephone consultation or follow-up epilepsy clinic appointment to establish improvements or resolution on BRV cessation.

2.3. Primary outcomes

Our primary outcomes were the proportion of 50% responders (defined as the proportion of patients with a 50% reduction in seizure frequency compared with baseline) and the proportion of seizure-free (defined as the proportion of patients who become seizure-free over the treatment period).

2.4. Secondary outcomes

Secondary outcomes included the proportion withdrawing for inefficacy, AEs, or both. We did not prespecify any AE of interests. We considered one AE (aggression) to be synonymous with another (irritability); thus, this has been presented as aggression in this paper.

2.5. Statistical analyses

Descriptive and frequency statistics were calculated for baseline demographics and baseline epilepsy information.

For primary efficacy outcomes, we calculated changes in seizure frequencies using the last three months of follow-up data and compared frequencies to a retrospective three-month baseline.

For all outcomes of interest, we performed the following subanalyses and compared outcomes for these categorical variables using chi-squared test with a significance level of $p < 0.05$:

A. Psychiatric or behavioral comorbidities/no psychiatric or behavioral comorbidity, and
B. Intellectual disability/no intellectual disability.

3. Results

3.1. Baseline characteristics

In total, 134 patients were prescribed BRV over the study period. All 134 patients had previously been prescribed LEV of which 63 were taking LEV at the time of treatment initiation. All 63 patients were withdrawn off LEV gradually and switched over to BRV.

Brivaracetam was used off-license in 25 patients with generalized epilepsy and seven patients with combined focal and generalized epilepsy.

Seventy-three (54%) patients had a psychiatric or behavioral disorder history. Out of the 73 patients, 34 (47%) had a diagnosis of depression or anxiety disorder and four (6%) had other psychiatric disorders (two schizophrenia, one bipolar disorder, and one obsessive–compulsive disorder). Forty-one patients had diagnosed intellectual disability. Of these, 35 (48%) had behavioral issues specifically documented in formal clinic correspondence (three Asperger syndrome, four autism, twenty verbal and/or physically aggressive behavior, six poor compliance/resistance to care, two reduced/poor social interaction). Seven patients had a combination of two or more of these issues.

The baseline characteristics are summarized in Table 1.

Table 1
Baseline characteristics.

Characteristics	(n = 134)
Age (years) [range(mean)]	17–71 (40)
Male/female	57/80
Age at epilepsy diagnosis (years) [range(mean)]	0–58 (14)
Duration of epilepsy (years) [range(mean)]	1–67 (25)
Proportion with intellectual disabilities (%)	31%
Proportion with psychiatric/behavioral disorder (%)	54%
Epilepsy type [frequency (%)]	
Focal epilepsy	102 (76)
Generalized epilepsy	25 (19)
Combined generalized and focal epilepsy	7 (5)
Number of previously tried AEDs [frequency (%)]	
2–3	6 (5)
4–6	33 (24)
7–9	70 (52)
10–11	25 (19)
Number of concomitant AEDs [frequency (%)]	
1	15 (11)
2	67 (50)
3	45 (34)
4	7 (5)
Concomitant AEDs [frequency (%)]	
LEV (all switched)	63 (47)
Carbamazepine	48 (36)
Sodium valproate	35 (26)
Lamotrigine	27 (20)
Pregabalin	23 (17)
Zonisamide	18 (13)
Topiramate	17 (13)

3.2. Primary outcomes

Patients were treated with BRV for a mean of 11 months (0.5–26 months) at a median dose of 200 mg (range: 50–200 mg).

A ≥50% responder rate was achieved in thirty (29%) patients with focal epilepsy, ten (25%) with generalized epilepsy, and five (71%) with combined focal and generalized epilepsy. Analysis of the overall ≥50% responder rate and proportion achieving seizure freedom did not demonstrate any statistical significance ($p = 0.06$). Seizure freedom was achieved in seven (7%) patients with focal epilepsy and four (16%) patients with generalized epilepsy ($p = 0.23$).

A subanalysis comparing the proportion of ≥50% responders according to the presence or absence of psychiatric and/or behavioral disorders did not demonstrate any statistically significant difference [29% vs. 39% ($p = 0.19$)].

A ≥50% responder rate was achieved in 15 (37%) of patients with intellectual disability. A subanalysis comparing the proportion of ≥50% responders according to the presence or absence of intellectual disability did not demonstrate any statistically significant difference [37% vs. 32% ($p = 0.63$)].

3.3. Secondary outcomes

3.3.1. Withdrawals

Brivaracetam was withdrawn in 49 (37%) patients; 22 (16%) patients due to lack of efficacy and 27 (21%) due to AEs. Fifteen (11%) patients reported an increased seizure frequency with BRV. Overall, 85 (63%) of patients remained on BRV at the end of the study period.

A subanalysis comparing the proportion of withdrawals according to the presence or absence of psychiatric and/or behavioral disorders did not demonstrate any statistically significant difference overall [40% vs. 33% ($p = 0.68$)] or for the proportion withdrawing because of AEs [38% vs. 30% ($p = 0.68$)].

A subanalysis comparing withdrawals according to the presence or absence of intellectual disability did not demonstrate any statistically significant difference overall [34% vs. 38% ($p = 0.36$)] or for the proportion withdrawing because of AEs [32% vs. 37% ($p = 0.36$)].

3.3.2. Tolerability

In total, eighty-four (63%) patients were documented to have at least one reported AE in the 26-month treatment period with 27 (20%) patients discontinuing BRV and withdrawing from the study because of one or more AE.

Overall, the most common AEs were sedation and somnolence reported in 35 (26%) patients. The commonest psychiatric/behavioral AEs were aggression (31 patients, 23%) and depression (16 patients, 12%) with 105 (78%) patients reporting more than one AE. Sedation, somnolence, and aggression were the commonest AEs leading to withdrawal of treatment. A full list of reported AEs and their frequencies are reported in Table 2.

Thirty-five patients reported new AE of sedation and somnolence. Fifteen (43%) patients remained on BRV because of improvement in seizure control. In the remaining 20 patients, 17 (85%) improved on discontinuing BRV, 2 (10%) unchanged, and 1 patient was lost to follow-up.

Thirty-one patients reported aggression. Seventeen (55%) patients had preexisting documented challenging and verbal/physically aggressive behavior. Of these, 7 had diagnosed intellectual disability (2 autism, 2 Asperger's, 1 tuberous sclerosis, 1 Lennox–Gastaut syndrome, 1 anoxic brain injury). In the other 10 patients, 5 had a concomitant diagnosis of depression/anxiety disorder. Twelve (71%) of the 17 patients reported unchanged aggressive behavior, with 5 (2 autism, 3 preexisting verbal/physically aggressive behavior) reporting worsened aggression on BRV, necessitating withdrawal of therapy. All 12 patients with unchanged aggression remained on BRV because of improvement in seizure control. All 5 patients with worsened aggression reported improvement on BRV withdrawal.

Table 2
Summary of reported AEs; n = 134.

Tolerability profile	Patients, n (%)
≥1 reported AE	105 (78)
Discontinuation of BRV due to AE	27 (20)
Reported AE	
Sedation/somnolence	35 (26)
Aggression	31 (23)
Depression	16 (12)
Increased seizure frequency	14 (11)
Dizziness	13 (10)
Gastrointestinal disturbance (nausea/vomiting/diarrhea)	9 (7)
Insomnia	7 (5)
Anorexia	5 (4)
Headache	4 (3)
Weight gain	3 (2)
Pruritus	2 (2)

Fourteen (45%) patients reported new AE of aggression. Following discontinuation of BRV, six (43%) reported improvement in aggression, six (43%) unchanged, and one (7%) worsened following discontinuation of BRV. One patient was lost to follow-up.

Sixteen patients reported AE of depression. Four (25%) had no prior history of depression. Of these patients, three (75%) reported resolution of low mood and one (25%) unchanged on stopping BRV. The remaining twelve (75%) had a preexisting diagnosis of depression with reported worsening depressive symptoms. Two (17%) remained on BRV because of improvement in seizure frequency. In the remaining 10, eight (80%) reported improvement and two (20%) unchanged following discontinuation of BRV.

3.4. Brivaracetam versus levetiracetam

All 134 patients had previously been prescribed LEV but experienced treatment failure, however, only 63 (47%) patients directly switched from LEV to BRV during the study. In the remaining 71 patients, LEV had been switched to a different AED prior to the study period. The commonest reasons for treatment failure on LEV overall were lack of efficacy (79/134; 59%), aggression (44/134; 33%), new or worsened symptoms of depression (13/134; 10%), sedation and somnolence (8/134; 6%), and insomnia (6/134; 5%).

In the 44 patients who previously reported aggression on LEV, we observed 17 (39%) patients experiencing the same when taking BRV and 27 (61%) patients reported no aggression. In the remaining 90 patients who reported no history of aggression with LEV, 14 (16%) patients experienced aggression on BRV. Treatment-related aggression due to LEV may not predict the likelihood of aggression with BRV irrespective of whether the patient has associated psychiatric/behavioral issues or intellectual disability. The results are presented in Table 3.

In the 63 patients directly switched to BRV during the study, LEV was withdrawn because of inefficacy in 38 (62%) patients. Following treatment with BRV, 28 (74%) reported no change to their seizure frequency, 9 (24%) reported improvement, and 1 (3%) reported worsened seizure control. One (3%) patient who reported improvement in seizure control had to withdraw BRV because of AE of aggression.

Seven (11%) of the 63 patients were switched from LEV to BRV because of an AE of worsened depressive symptoms on LEV. Five (71%) had a preexisting diagnosis of depression. Of these 5 patients, 3 (60%) improved on stopping BRV and the remaining 2 (40%) reported further worsened depressive symptoms. In the 2 patients with no previous history of depression, both reported resolution of depressive symptoms on switching to BRV.

Five (8%) of the 63 patients switched to BRV during the study because of sleep disruption on LEV (2 sedation and somnolence, 3

Table 3
Incidence of aggression between patient groups with previous LEV therapy and new or unchanged aggression on switching to BRV.

	Preexisting psychiatry/behavioral disorder (n = 73)	No psychiatric/behavioral history (n = 61)	Diagnosed intellectual disability (n = 41)	No intellectual disability (n = 93)
Previous aggression improved on BRV [frequency (%)]	13 (18)	14 (23)	8 (20)	19 (20)
Previous aggression not improved on BRV [frequency (%)]	11 (15)	6 (10)	7 (17)	10 (11)
New aggression on BRV [frequency (%)]	6 (8)	8 (13)	3 (7)	11(12)
No aggression on LEV or BRV [frequency (%)]	43 (59)	33 (54)	23 (56)	53 (57)

insomnia). All 5 patients reported symptomatic improvement on switching to BRV.

The majority of patients switching from LEV to BRV because of psychiatric or behavioral AE reported an improvement to their symptoms. Patients with preexisting psychiatric disorder or intellectual disability with previous aggression on LEV appear more likely to have similar issues on BRV compared with those without similar preexisting comorbidities, however, this was not statistically significant. Brivaracetam was stopped in all 3 patients with intellectual disability who developed AE of aggression following therapy switch because of the high risk of injury to self and the patient's carers.

Seven patients reported symptoms of depression on LEV. Six patients had preexisting diagnosis of depression and complained of worsened symptoms on LEV. In these 10 patients, six (60%) reported improvement to their mood symptoms, three (30%) stopped BRV because of worsened mood symptoms, and one (10%) stopped because of excessive sedation. In the remaining 5 patients reporting new symptoms of depression without previous psychiatric comorbidity, all 5 improved following a switch from LEV to BRV.

Three patients reported intolerable AE of sedation on LEV. All 3 reported symptomatic improvement on switching to BRV.

4. Discussion

To the best of our knowledge, this is the largest single-center prospective cohort study assessing overall efficacy, tolerability, and AE profile in the United Kingdom over an extended period of time.

The percentage of patients with focal epilepsy with ≥50% responder rate was lower than reported in the phase IIb/III clinical trials and long-term follow-up studies [5–8]. This could be explained by the drug resistance in our patient with epilepsy cohort. More than 70% of patients had previously tried between 7 and 11 different AEDs, and 89% of patients were on two or more concomitant AEDs prior to commencing BRV.

In patients with generalized and combined focal and generalized epilepsy where BRV was used off-license, a ≥50% responder rate of 47% was observed. This was also noted in a previous randomized controlled trial and case report suggesting improvement in seizure frequency, ≥50% responder rate, and seizure freedom rate compared with placebo [12]. This could possibly be attributed to the higher potency of BRV as a SV2A inhibitor compared with LEV. The more favorable AE profile may also have contributed to improved compliance and a better response rate. This, however, needs to be interpreted with caution because of the small sample size. Our study did not demonstrate any statistically significant difference for efficacy outcomes when comparing patients according to the presence or absence of psychiatric and/or behavioral disorder, or intellectual disability.

Our study demonstrated a higher AE incidence compared with previous studies, in particular of sedation, somnolence, aggression, and depression. The AEs in the majority of patients resolved following discontinuation of BRV therapy. Brivaracetam therapy was continued in a number of patients despite the AEs because of improvement in seizure control outweighing the impact of the AEs. More than half of the recorded AEs were reported and documented after 4 months, up to 11 months. We did not find any significant difference in tolerability between patients with preexisting psychiatric or behavioral comorbidities, or intellectual disability in comparison with those without these conditions. Aggression and depression were more often reported as AEs if there was a pretreatment diagnosis of these comorbidities.

We collected data over a 26-month period compared with a recent meta-analysis that only included studies ranging between 7 and 16 weeks [8]. The higher AE incidence from our study may suggest that these AEs manifest later in the treatment stage hence, the importance of revisiting and addressing any AE on subsequent patient follow-up reviews. This may be an aspect that warrants further study.

The majority of patients switching from LEV to BRV because of psychiatric or behavioral AE reported an improvement to their symptoms. Patients with preexisting psychiatric disorder or intellectual disability with previous AE of aggression on LEV appear more likely to have similar issues on BRV compared with those without similar preexisting comorbidities, however, this was not statistically significant.

In patients switching directly from LEV to BRV, the majority of patients reported no change to their seizure control, however, our study suggests that patients who discontinued LEV may still benefit from a switch to BRV due to the improved AE profile that may improve compliance and quality of life.

The limitations of this study were the open-label design and relatively small study size compared with previous randomized controlled trials. The patients were assessed by three different neurologists, with potential interobserver variations.

5. Conclusion

Overall, our study suggests that BRV may be a useful adjunctive treatment for patients with focal or generalized epilepsies. Given the fewer AED options available to patients with generalized epilepsies, our results would support further efficacy studies in this patient population. There is, however, a higher incidence of sedation, somnolence, and aggression across all patient groups, hence, patient education and caution needs to be exercised when considering BRV particularly in patients with preexisting depression and behavioral disorders. Patients who have discontinued LEV may still benefit from BRV despite the lower than expected improvement to seizure control given the potential benefits from an AE perspective. The results, however, should be interpreted with considerations towards the small sample size, open-label design, absence of a standardized measure of AEs, and potential interobserver variation. Therefore, findings from further studies considering these potential confounders would be of interest.

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Declaration of Competing Interest

None of the authors have any conflict of interest to disclose. We confirm that we have read and understood the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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