

Retention of brivaracetam in adults with drug-resistant epilepsy at a single tertiary care center

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ABSTRACT

Introduction: Brivaracetam (BRV) is licensed as an adjunctive treatment for focal epilepsy. We describe our clinical experience with BRV at a large UK tertiary center.

Methods: Adults initiated on BRV between July 2015 and July 2020 were followed up until they discontinued BRV or September 2021. Data on epilepsy syndrome, duration, seizure types, concomitant and previous antiseizure medication (ASM) use, BRV dosing, efficacy, and side effects were recorded. Efficacy was categorized as temporary (minimum three months) or ongoing (at last follow-up) seizure freedom, $\geq 50\%$ seizure reduction, or other benefits (e.g., no convulsions or daytime seizures). Brivaracetam retention was estimated using Kaplan–Meier survival analysis.

Results: Two-hundred people were treated with BRV, of whom 81% had focal epilepsy. The mean (interquartile range [IQR]) follow-up time was 707 (688) days, and the dose range was 50–600 mg daily. The mean (IQR) of the previous number of used ASMs was 6.9 (6.0), and concomitant use was 2.2 (1.0). One-hundred and eighty-eight people (94%) had previously discontinued levetiracetam (LEV), mainly due to side effects. 13/200 (6.5%) were seizure free for a minimum of six months during treatment, and 46/200 (23%) had a $\geq 50\%$ reduction in seizure frequency for six months or more. Retention rates were 83% at six months, 71% at 12 months, and 57% at 36 months. Brivaracetam was mostly discontinued due to side effects (38/75, 51%) or lack of efficacy (28/75, 37%). Concomitant use of carbamazepine significantly increased the hazard ratio of discontinuing BRV due to side effects ($p = 0.006$). The most commonly reported side effects were low mood (20.5%), fatigue (18%) and aggressive behavior (8.5%). These side effects were less prevalent than when the same individuals took LEV (low mood, 59%; aggressive behavior, 43%). Intellectual disability was a risk factor for behavioral side effects ($p = 0.004$), and a pre-existing mood disorder significantly increased the likelihood of further episodes of low mood ($p = 0.019$).

Conclusions: Brivaracetam was effective at a broad range of doses in managing drug-resistant epilepsy across various phenotypes, but less effective than LEV in those who switched due to poor tolerability on LEV. There were no new tolerability issues, but 77% of the individuals experiencing side effects on BRV also experienced similar side effects on LEV.

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1. Introduction

Approximately 1 in 3 people with epilepsy fail to become seizure free after treatment with two appropriate antiseizure medications (ASMs) [1], resulting in significant morbidity, mortality, and

lower quality of life [2]. Brivaracetam (BRV), an analog of levetiracetam (LEV), is licensed as an adjunctive treatment for focal epilepsy since 2015. Brivaracetam binds to the synaptic vesicle protein 2A via a different target site with a higher affinity than LEV [3–5]. Phase III trials suggested efficacy in people with drug-resistant focal epilepsy [6–8] with a lower incidence of neuropsychiatric side effects than LEV [9].

Data on “real world” experiences are an essential complement to regulatory trials. Our group has extensive experience assessing

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the retention of new ASMs as we have carried out these assessments since the 1990s [10–15]. We have now evaluated the effectiveness, retention, and tolerability of BRV in adults with various epilepsy syndromes followed up for up to 6 years, including its use at higher doses and those with intellectual disabilities.

2. Material and methods

This was an observational study of adults 17 years and older with epilepsy who received their first prescription for BRV at the epilepsy specialist clinics at the National Hospital for Neurology and Neurosurgery (Queen Square and Chalfont sites) between July 2015 and July 2020. They were followed up until they discontinued BRV or until September 2021. They were identified in the central pharmacy prescription records and the departmental clinical database. Using the electronic health record system, we collected: demographic and baseline clinic information (including epilepsy syndrome and seizure type, any previous epilepsy surgery or vagal nerve stimulator, the presence/absence of intellectual disability or coexistent mental health conditions, and previous and current ASMs), response to LEV (including the effect on seizure frequency and side effects), BRV dose, duration of treatment, impact on seizure frequency, other clinical benefits (improvement in concentration, mood, seizure severity), reported adverse events (general physical and neuropsychiatric), reasons for discontinuing BRV, and concomitant medication changes made while on BRV. Seizure frequency was binarized into these mutually inclusive categories: seizure freedom (for a minimum of 6 months), $\geq 50\%$ reduction, any seizure reduction, and seizure aggravation during treatment. Individuals were asked about side effects in the clinic, and responses were qualitatively collected and categorized according to themes. One condition of BRV prescription in our center was that LEV had previously been tried with some benefits being observed, but the individual had discontinued it due to tolerability issues, with some exceptions.

SPSS (SPSS, Inc.) was used for statistical analysis, and SPSS and GraphPad Prism (GraphPad, Inc.) were used to produce figures. We used Kaplan–Meier survival analysis to estimate retention rates of BRV. We used a binary logistic regression model to ascertain how increasing drug dose (independent continuous variable) affected side-effect prevalence (dependent binary variable). Two binary logistic regression models were also used to assess whether certain covariates were associated with behavioral change (model one) and low mood (model two, both binary dependent variables) on BRV. We chose categorical covariates as independent variables for these two models. We thought they would have the strongest influence on behavioral change and low mood: sex, presence of intellectual disability, having an established psychiatric disorder, and previously experiencing behavioral change or low mood on LEV. We used Cox regression analysis to assess the impact of different covariates on drug retention. We used two models, one investigating the effects of concomitant medication (the most prescribed medications were chosen, all were coded as binary independent variables) and another exploring the impact of clinical and demographic features (continuous independent variable: age; categorical independent variables: sex, presence of intellectual disability, experiencing side effects, and experiencing seizure freedom on BRV) on the hazard ratio of discontinuing BRV. We chose these independent variables because we thought they were most likely to be associated with drug retention.

Our Clinical Audit and Quality Improvement Committee approved this project as an audit of outcomes to inform the place of BRV in the antiseizure armamentarium.

3. Results

3.1. Cohort characteristics and previous response to LEV

We included 200 people (385 patient-years exposure), and the mean (SD) study follow-up time on BRV was 707 (520) days. The median was 647 days and interquartile range (IQR) was 688 days (Q1 = 263, Q3 = 951 days). The mode starting up-titrated dose of BRV was 100 mg total per day, and mode maximum trialled dose was 200 mg total per day (total range 50–600 mg, 1st quartile 150 mg, 3rd quartile 300 mg; Fig. 1). 47/200 (23.5%) underwent concomitant treatment changes after starting BRV during follow-up. Focal impaired awareness seizures were the most common seizure type (Table 1). One-hundred eighty-eight people had previously trialled LEV for a mean of 6.2 years at a median total dose of 2000 mg per day. Reasons for discontinuing LEV were: behavioral disturbance, including aggressive behavior or irritability (81/188, 43%), low mood (111/188, 59%), cognitive disturbance (8/188, 4.3%), and general physical symptoms (e.g., fatigue, headache; 46/188, 24.5%). Four people were seizure free on LEV before starting BRV.

3.2. Effectiveness of BRV

The effectiveness of BRV on seizure frequency is shown in Table 2. Two of the four seizure-free people on LEV suffered a seizure relapse after switching to BRV. While 44 of 200 (22%) reported a period of seizure aggravation during treatment, this was sustained and led to drug discontinuation in 16 (8%). Individuals described improvements other than improved seizure control when taking BRV compared to LEV, including improved mood (25/200, 12.5%), less challenging behavior (15/200, 7.5%), having more energy (15/200, 7.5%), and improved cognition (8/200, 4%). Of the 31 individuals with genetic generalized epilepsy, four were seizure free, with seven having a $>50\%$ reduction in seizures and 21 reporting a decrease in seizure frequency.

3.3. Retention and side effects from BRV

The duration of BRV treatment ranged from 2 days to 6.2 years. Retention rates during the first 36 months of treatment are shown in Fig. 2 and Table 3. Reasons for stopping BRV included side effects (38/75, 51%), no benefit (28/75, 37.3%), and seizure aggravation (16/75, 21.3%). A range of general physical and neuropsychiatric

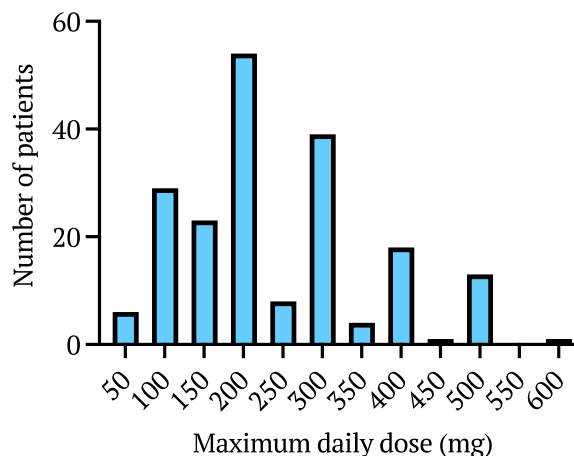


Fig. 1. Frequency distribution of total daily doses of BRV.

Table 1
Clinical and demographic information.

Characteristic	Statistic
Female, <i>n</i> (%)	120 (60)
Age at review, mean years (SD)	41.0 (14)
Age at epilepsy diagnosis, mean years (SD)	14.1 (12)
Syndrome, <i>n</i> (%)	
Symptomatic Focal	63 (31.5)
Cryptogenic Focal	98 (49)
Idiopathic Generalized	31 (15.5)
Symptomatic Generalized	3 (1.5)
Other	5 (2.5)
Seizure type, <i>n</i> (%)	
Focal Aware	56 (28)
Focal Impaired Awareness	143 (71.5)
Focal to Bilateral	94 (47)
Generalized Motor	
Tonic-Clonic	33 (16.5)
Tonic	10 (5)
Atonic	8 (4)
Myoclonic	23 (11.5)
Generalized Nonmotor (Absence)	26 (13)
Other	32 (16)
Intellectual disability, <i>n</i> (%)	63 (31.5)
Previous epilepsy surgery, <i>n</i> (%)	38 (19)
Vagal nerve stimulator in situ, <i>n</i> (%)	38 (19)
Established mood or anxiety disorder, <i>n</i> (%)	110 (55)
Previous antiseizure medication, mean (SD)	6.9 (4.5)
Additional current antiseizure medication, mean (SD)	2.2 (1)

For all percentages, the denominator was 200 (our full sample size).
SD = Standard Deviation.

Table 2
Effectiveness of BRV on seizure frequency at follow-up.

Subset	Seizure Free (%)	≥50% reduction (%)	Any reduction (%)
Whole cohort	13/200 (6.5)	46/200 (23)	102/200 (51)
Focal epilepsy	9/161 (6)	39/161 (24)	81/161 (50.5)
Generalized epilepsy	4/39 (10.5)	7/39 (18)	21/39 (54)
Intellectual disability	3/63 (5)	13/63 (20.5)	34/63 (54)
Direct switchers	8/76 (10.5)	22/76 (28.9)	45/76 (59.2)

Table 3
Retention rates of brivaracetam treatment.

Duration (months)	Retention estimate (%)	Standard error (%)
6	83	2.7
12	72	3.2
18	66	3.4
24	61	3.6
36	57	4.0

Table 4
Reported adverse events.

Adverse effect	<i>n</i> (%)
Low mood	41 (20.5)
Tiredness or fatigue	36 (18)
Aggressive behavior	17 (8.5)
Unsteadiness	13 (6.5)
Anxiety	12 (6)
Impaired cognition	11 (5.5)
Irritability	10 (5)
Nausea or loss of appetite	9 (4.5)
Skin rash	8 (4)
Suicidal or self-harm ideation	7 (3.5)
Headache	5 (2.5)
Tremor	5 (2.5)
Insomnia	5 (2.5)
Psychosis	3 (1.5)
Other side effects	24 (12)

For all percentages, the denominator was 200 (our full sample size).

side effects was observed (Table 4). We used a binomial logistic regression to investigate how increasing total daily doses of BRV affected the likelihood of experiencing drug side effects. This suggested that increasing doses were associated with a small but significant reduction in side effect prevalence (Exp (B) 0.996 [0.993–0.999], *p* = 0.004). Lastly, we tested the effects of several covariates on the retention of BRV (Table 5).

3.4. Neuropsychiatric side effects of BRV

Using binary logistic regression, we assessed whether several covariates affected the likelihood of developing low mood or

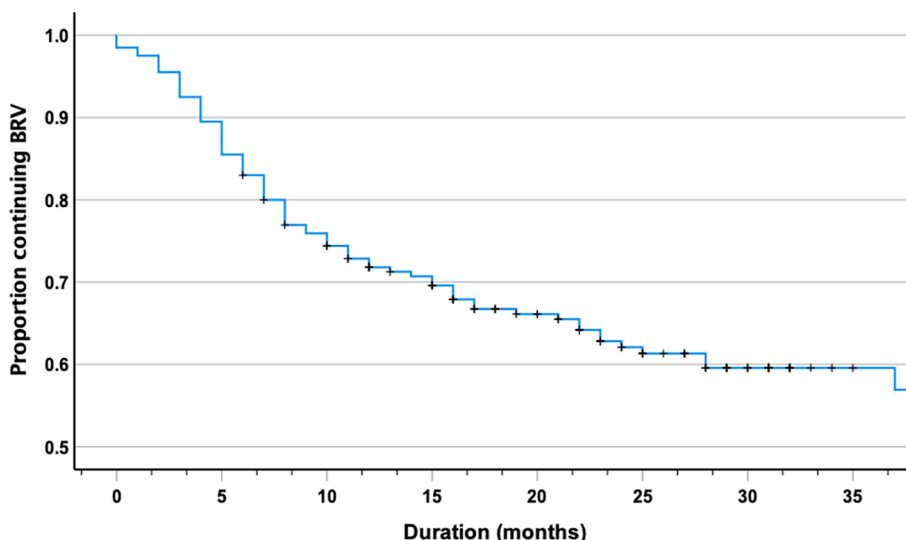


Fig. 2. Retention of brivaracetam. This Kaplan–Meier plot shows the estimated retention of BRV during the first 36 months of treatment.

Table 5
Factors affecting retention of BRV.

Covariate	Hazard ratio of discontinuing BRV (95% CI)	<i>p</i>
Concomitant medication		
Carbamazepine (<i>n</i> = 42, 21%)	2.85 (1.34–6.06)	0.006**
Lamotrigine (<i>n</i> = 50, 25%)	1.63 (0.75–3.57)	0.218
Valproate (<i>n</i> = 38, 19%)	1.37 (0.54–3.49)	0.504
Perampanel (<i>n</i> = 12, 6%)	1.13 (0.38–3.36)	0.831
Zonisamide (<i>n</i> = 22, 11%)	1.05 (0.31–3.53)	0.943
Lacosamide (<i>n</i> = 35, 17.5%)	0.94 (0.32–2.77)	0.910
Oxcarbazepine (<i>n</i> = 23, 11.5%)	0.76 (0.18–3.27)	0.714
Clinical outcome or demographic		
Female (<i>n</i> = 120, 60%)	1.63 (0.70–3.77)	0.255
Intellectual disability (<i>n</i> = 63 (31.5%))	1.37 (0.62–3.02)	0.435
Side effects (<i>n</i> = 114, 57%)	1.21 (0.55–2.63)	0.637
Age	0.99 (0.97–1.02)	0.756
Seizure freedom (<i>n</i> = 13, 6.5%)	0.55 (0.08–4.10)	0.562

Univariate cox regression analyses to investigate the effects of concomitant medication or clinical/demographic factors on the hazard ratio of discontinuing BRV.

** *p* < 0.01.

Table 6
Predictors of neuropsychiatric side effects from BRV.

Outcome variable	Covariate	Hazard Ratio (95% CI)	<i>p</i>
Behavioral change on BRV	Intellectual disability	3.62 (1.50–8.74)	0.004*
	Established psychiatric disorder	1.28 (0.54–3.06)	0.574
	Behavioral change on LEV	1.00 (0.42–2.39)	0.994
	Low mood on LEV	0.64 (0.27–1.49)	0.298
	Female Sex	0.43 (0.18–1.03)	0.057
Low mood on BRV	Established psychiatric disorder	2.02 (1.12–3.65)	0.019*
	Intellectual disability	1.80 (0.95–3.39)	0.072
	Behavioral change on LEV	0.72 (0.40–1.30)	0.272
	Female Sex	0.59 (0.33–1.08)	0.086
	Low mood on LEV	0.56 (0.31–1.00)	0.048*

CI = confidence interval.

* *p* < 0.05.

behavioral side effects (Table 6). Overall model fit (Hosmer–Lemeshow test for goodness-of-fit) was significant when low mood (chi-square_{df} 14.645₅, *p* = 0.012) and behavioral side effects (chi-square_{df} 11.649₅, *p* = 0.040) were used as dependent variables. Having an intellectual disability significantly increased the likelihood of becoming irritable or aggressive on BRV (hazard ratio (95% CI) 3.62 (1.50–8.74), *p* = 0.004). An established mood or anxiety disorder significantly increased the likelihood of developing low mood on BRV (hazard ratio (95% CI) 2.02 (1.12–3.65), *p* = 0.019). We also found that people who complained of low mood from LEV treatment were less likely to complain of low mood on BRV (hazard ratio (95% CI) 0.56 (0.31–1.00), *p* = 0.048).

To investigate drug cross-over effects, we compared side-effect prevalence between people who had switched directly from LEV to BRV because of side effects (*n* = 76) versus those who had previously taken LEV but not within one month of starting BRV (*n* = 112). There was no significant difference between these groups (26.7% vs 38.9%, chi-square_{df} 3.023₁, *p* = 0.087). Therefore, no evidence of a cross-over effect for mood or behavioral side effects was observed. In those directly switching from LEV, the prevalence of general physical side effects was significantly lower (20.0% vs 51.3%, chi-square_{df} 18.626₁, *p* < 0.001). There was no difference in the likelihood of discontinuing BRV between direct and non-direct switchers (chi-square_{df} 0.053₁, *p* = 0.818).

4. Discussion

We assessed outcomes of BRV treatment for refractory epilepsy at a single tertiary center. A broad range of clinical phenotypes were evaluated, including people with generalized epilepsy, on more concomitant medications and over more extended follow-up periods, making this cohort more heterogeneous than previous observational studies [16–25]. Most of the cohort had previously discontinued LEV due to tolerability issues.

Brivaracetam was effective and well-tolerated in this drug-resistant cohort, with acceptable retention rates over 36 months of treatment. Our responder rate is comparable to previous cohort studies [16–25]. For instance, a study reported a responder rate of 53.7% at 36 months [25], comparable to our rate of 57%. The retention rates in this cohort, of 57% at 36 months, were higher than those observed in our historical cohort of people on perampanel (43%) and lacosamide (35%) [26,27]. The comparable rate at 36 months for LEV in our series was 58% [28]; however, our current cohort was smaller and consisted almost entirely of people who had previously discontinued LEV.

The similarity in responder rates between focal and generalized epilepsy syndromes is in keeping with a recent report [21]. In contrast to previous studies, we observed similar responder rates between people with and without intellectual disability [21,22].

During the first six-month follow-up, almost a fifth discontinued BRV, most commonly due to side effects, no improvement in seizure activity, and seizure exacerbation. Two of the four seizure-free people on LEV who were switched over to BRV experienced further seizures. We found that concomitant use of carbamazepine was significantly associated with discontinuation of BRV while clinical outcomes, demographics, and other concomitant ASM use were not. Interestingly oxcarbazepine, a structural derivative of carbamazepine, did not share this association. Carbamazepine and oxcarbazepine are metabolized differently by the cytochrome P450 system to their primary active metabolites (carbamazepine-10,11-epoxide for carbamazepine and 10-monohydroxy derivative carbamazepine); [29,30]). The link between carbamazepine use and discontinuation of BRV could relate to the adverse neurological effects associated with carbamazepine-10,11-epoxide [31].

Side-effect profiles were comparable to previous reports [9]. Skin rash during BRV treatment has been previously reported in a cohort study, with similar prevalence [21], but not in an extensive, pooled analysis of clinical trials [9]. Skin rashes observed included maculopapular rash, some requiring dermatological review. We did not find that side-effect prevalence increased with higher doses of BRV, suggesting that higher drug doses within our treatment range are tolerable.

Levetiracetam is associated with neuropsychiatric side effects, including low mood, aggression, and irritability. A frequency of 10% was reported [32], which can be severe enough to lead to dose reduction or drug discontinuation [33]. We cannot comment on differences in the prevalence of neuropsychiatric side effects in people naïve to BRV and LEV. Neuropsychiatric side effects seem less prevalent on BRV than when the same individuals took LEV. This is consistent with recent observational cohort studies [34–36], including data from people who had directly switched drugs or had previous LEV exposure, suggesting that BRV has a favorable side-effect profile. These improvements may reflect reductions in seizure frequency and off-target pharmacodynamic effects. We also observed that those reporting low mood on LEV were significantly less likely to report this on BRV. This may be due to different affinities between these medications at various central neurotransmitter receptors [37]. Alternatively, this may reflect confirmation bias since BRV was associated with less mood disturbance than

LEV before starting treatment. Lastly, we found that people with intellectual disabilities were significantly more likely to have behavioral disturbances on BRV. This reflects the increased prevalence of challenging behaviors among people with an intellectual disability [38] and underscores the importance of training in managing challenging behavior [39].

One possible reason for the high retention of BRV could be that no new ASM had been licensed since BRV until the study ended. The lack of further pharmacological options may have contributed to the duration of BRV therapy. Furthermore, most individuals switching from LEV to BRV did so due to tolerability issues instead of a lack of efficacy with the former. Therefore, those in whom the adverse effects were mitigated were more likely to persevere on BRV.

Our report provides one of the most extended follow-up periods and the widest dose range compared to previous reports. Almost all people in our cohort had previously trialed and discontinued LEV. We, therefore, assessed a group with relatively high side-effect prevalence, who are more likely to reflect real-life BRV candidates compared with LEV-naïve groups. This also allowed us to make within-subject observations on the relative effectiveness and side-effect profile between BRV and LEV.

Our study has limitations. As deriving from an observational cohort, our data are not directly powered to compare BRV and LEV. This should be a subject for future investigation, especially comparing their efficacy and tolerability at varying doses, seizure freedom rates, and effect on specific epilepsy syndromes. Retrospective data on seizure count are also subject to recall bias. Due to the high proportion of concomitant treatment changes, perhaps not unexpected considering the length of follow-up and the refractory nature of epilepsy in this cohort, it is also difficult to directly ascribe all changes in seizure frequency and side effects to BRV alone. Lastly, while we investigated how drug dose was associated with side-effect prevalence, we did not grade side-effect severity and therefore did not investigate the relationship between drug dose and side-effect severity.

In conclusion, we provide observational evidence for good retention, responder rates, and neuropsychiatric side-effect prevalence of variable BRV treatment doses in a heterogeneous, pharmaco-resistant cohort. Our real-world data supplement trial data and could be generalized to a clinic setting, especially for people with epilepsy who have not tolerated LEV therapy.

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Declarations of interest

JWS reports personal fees as speaker or consultant from Arvelle, Eisai, GW Pharmaceuticals, UCB Pharma, and Zogenix. MJK reports

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