



Brief Communication

Brivaracetam in adults with drug-resistant epilepsy and psychiatric comorbidities

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ABSTRACT

This is a case series of 25 patients with drug-resistant epilepsy and psychiatric comorbidities who started on brivaracetam (BRV) at St George's University Hospitals and Frimley Health in London. Median BRV dose was 150 mg for a median follow-up period of 8 months. Twenty had focal epilepsy, four had generalized epilepsies, and one had unclassified epilepsy; 76% had mood disorders (either depression or bipolar disorder), 12% intellectual disabilities with autism spectrum disorder and challenging behavior, and 12% psychoses. Forty percent of patients presented at least 50% seizure reduction, but none of them became seizure-free. A total of 44% of patients discontinued BRV, 20% because of adverse events, 20% because of inefficacy, and 4% because of both. Depression was reported by 8%, aggressive behavior by 8%, while 4% reported both. A total of 91.6% had received levetiracetam (LEV) before, in whom LEV was discontinued because of psychiatric adverse events (PAEs) in half. Seventy-seven percent of patients who developed PAEs with LEV did not do so on BRV suggesting that BRV is better tolerated than LEV in complex patients with psychiatric comorbidities and that the synaptic vesicle glycoprotein 2A (SV2A) protein modulation is unlikely to be implicated in LEV-related PAEs.

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1. Introduction

Brivaracetam (BRV) is a novel antiepileptic drug (AED), structurally related to levetiracetam (LEV). It is highly selective for the synaptic vesicle glycoprotein 2A (SV2A) with a 15–30 times higher affinity than LEV [1]. However, as compared with LEV, BRV also displays inhibitory activity at neuronal voltage-dependent sodium channels, and it does not seem to act on AMPA and high voltage-gated calcium channels [1].

It is well established that patients with epilepsy can experience treatment-emergent psychiatric adverse events (PAEs), and different AEDs seem to have a different potential for PAEs [2,3]. A rapid titration of the drug, a comorbid psychiatric disorder, and a diagnosis of drug-resistant temporal lobe epilepsy seem to be the most relevant risk factors for the development of PAEs [4–6].

Psychiatric problems are relatively common comorbidities in epilepsy [7]. Epidemiological studies show a uniformly increased prevalence of psychiatric disorders in those with epilepsy as compared with the general population and other long-term conditions [8]. This seems to partially reflect the severity of the seizure disorder. It is, therefore, evident that patients with drug-resistant epilepsy are more likely to have

psychiatric comorbidities, and consequently, they are at an increased risk of PAEs.

This is an audit of BRV in patients with drug-resistant epilepsy and psychiatric comorbidities, looking at standards of prescription and occurrence of PAEs.

2. Methods

Brivaracetam was licensed in the UK in March 2016. This is a retrospective review of clinical notes of all patients with drug-resistant epilepsy and psychiatric comorbidities on BRV attending the Outpatient Epilepsy Clinics at the Atkinson Morley Regional Epilepsy Centre, St George's University Hospital and Frimley Health between March 2016 and December 2017. Drug-resistant epilepsy was defined according to International League Against Epilepsy (ILAE) criteria [9] while psychiatric comorbidity was defined by a currently present psychiatric condition when BRV was started. This study was registered as an audit with the audit departments of both St George's University Hospitals and Frimley Health, and the use of anonymized information previously collected during standard clinical care is excluded from formal Research Ethics Committee review. Data storage and management was compliant with the Good Clinical Practice statement in accordance with the Declaration of Helsinki.

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Prescription of BRV (indication, titration, and maintenance dose) in every patient was reviewed. Clinical and demographic data were also collected from hospital notes. All side effects, including PAEs, were noted. Previous use of LEV, as well as reasons for LEV discontinuation including PAEs, was also documented.

3. Results

A total of 25 patients were included in this audit. The median duration of the follow-up was 8 months (range: 3–19).

Clinical and demographic data are shown in Table 1. Brivaracetam was prescribed as an adjunctive treatment to all patients apart from one patient who switched from LEV monotherapy to an off-label BRV monotherapy.

In terms of psychiatric comorbidities, most patients (76%) had a mood disorder with or without comorbid anxiety disorder; two patients had a previous history of suicidal attempts. A total of 4 patients (16%) had intellectual disabilities with autism spectrum disorder and challenging behavior.

In terms of previous exposure to LEV, only three patients (12%) had not been previously exposed, eight patients were switched from LEV to BRV directly, and 14 patients had tried and discontinued LEV in the past. In the LEV group (past and current), 59% of patients developed PAEs (in all cases, depression and/or aggressive behavior). Among those who switched directly from LEV to BRV, BRV was cross-titrated with LEV at

the same time in four cases, two patients had a sequential titration (LEV was discontinued, and then, BRV was started) while in two cases, BRV was switched directly from LEV overnight, the first one with a BRV:LEV ratio of 1:10, while in the second patient, a dose of LEV 750 mg twice daily was switched overnight to BRV 100 mg twice daily. For the remaining patients, the routine BRV initiation protocol consisted of 50 mg daily increasing by 50 mg increments every 2 weeks up to a maximum dose of 100 mg twice daily according to the clinical response. Median maximum dose of BRV was 150 mg/day with a range of 50 mg–200 mg. Median duration of BRV treatment was 8.5 months with a range from 1 month to 19 months. Concomitant AEDs and drug regime are shown in Table 1.

In terms of efficacy, 40% of patients presented at least 50% seizure reduction, but none of them became seizure-free; in one case, only tonic-clonic seizures were fully controlled. Seizure worsening was reported in 12% of cases. The median BRV dose in responders was 150 mg/day with a range of 100 mg–200 mg.

In terms of tolerability, a total of 44% of patients discontinued BRV, 20% because of adverse events, 20% because of inefficacy, and 4% because of both. Adverse events during treatment with BRV, including PAEs, are shown in Table 2. Five patients (20%) developed PAEs (mainly depressed mood and aggressive behavior), and two of them developed suicidal ideation in the context of depression. Among the 13 patients who previously tried LEV and developed PAEs, 77% of them did not do so on BRV. Among the nine patients who tried LEV and did not develop PAEs, only one developed depression on BRV.

Table 1
Clinical and demographic data of the sample.

	N = 25
Age, median years (range)	43 (18–68)
Gender	
Male	6 (24%)
Female	19 (76%)
Duration of the epilepsy, median years (range)	22 (8–58)
Epilepsy type	
Focal	20 (80%)
Generalized	4 (16%)
Unclassified	1 (4%)
Etiology	
Structural	10 (40%)
Genetic	7 (28%)
Immune	1 (4%)
Unknown	8 (32%)
Psychiatric comorbidities	
Mood and anxiety disorders in comorbidity	10 (40%)
Major depressive disorder only	7 (28%)
Bipolar disorder only	2 (8%)
Psychoses	3 (12%)
Intellectual disabilities with challenging behavior	3 (12%)
Antiepileptic drug (AED) treatment	
Previously failed AED, median (range)	4.5 (range: 1–13)
Number of concomitant AED, median (range)	3 (range: 1–4)
Monotherapy (%)	4 (16%)
Two AEDs (%)	12 (48%)
Three AEDs (%)	8 (32%)
Four or more AEDs (%)	1 (4%)
Concomitant AEDs	
Lamotrigine	14 (56%)
Clobazam	9 (36%)
Sodium valproate	6 (24%)
Pregabalin	5 (20%)
Carbamazepine	5 (20%)
Lacosamide	4 (16%)
Oxcarbazepine	4 (16%)
Zonisamide	4 (16%)
Clonazepam	1 (4%)
Ethosuximide	1 (4%)
Phenobarbitone	1 (4%)
Phenytoin	1 (4%)
Primidone	1 (4%)
BRV monotherapy	1 (4%)

4. Discussion

This is the first report, to our knowledge, describing in detail the PAEs of BRV in patients with drug-resistant epilepsy and psychiatric comorbidities who represent the highest risk population for PAEs.

A pool data analysis of Phase II and III studies report depression and irritability in about 7% and 5% respectively [10]. A systematic review and meta-analysis of randomized, placebo-controlled, single- and double-blind add-on studies of BRV showed that irritability is the only PAE statistically more common in treated patients than controls but also emphasizes that PAEs are the most common cause for drug discontinuation [11]. However, in controlled trials, patients with psychiatric comorbidities are often excluded.

Our data show that, overall, the occurrence of depression and aggressive behavior is not higher in patients with drug-resistant epilepsy and psychiatric comorbidities as compared with that in Phase II and III studies, clearly suggesting that BRV is well tolerated. This is further

Table 2
Treatment emergent adverse events during BRV.

	N = 25 (%)
Patients reporting at least one adverse event	10 (40%)
Discontinuation of BRV due to AEs	6 (24%)
Non-PAEs	
Upper Gastrointestinal (GI) symptoms	2 (8%)
Tiredness	1 (4%)
Dizziness	1 (4%)
Headache	1 (4%)
Breathing difficulties	1 (4%)
PAEs ^a	
Depression only	2 (8%)
Aggressive behavior only	2 (8%)
Depression and aggressive behavior	1 (4%)
Suicidal ideation	2 (8%)
PAEs in the subgroup with previous PAEs during LEV ^a	N = 13 (%)
Aggressive behavior only	2 (15%)
Depression and aggressive behavior	1 (8%)
Suicidal ideation	1 (8%)
No PAEs	10 (77%)

^a Patients can be counted in more than one group.

supported by the observation that around 77% of patients who had PAEs on LEV did not have any on BRV.

A better tolerability of BRV as compared with LEV was partially suggested by a 12-week, open-label, prospective, exploratory study of patients with epilepsy switching from LEV to BRV [12]. That study shows that 93.1% of patients had a reduction in nonpsychotic behavioral adverse events, and 62.1% went into remission. However, the primary endpoint was highly selective, as the authors focused on nonpsychotic behavioral adverse events only and did not provide any information on the previous psychiatric history of their patients. For all these reasons, that study could not be considered informative enough regarding PAEs during BRV therapy.

The better tolerability of BRV as compared with LEV, in terms of PAEs, is of great interest and poses further questions on the role of the modulation of the SV2A protein for PAEs with LEV. In fact, BRV is highly selective for the SV2A protein, and it has up to 30 times higher affinity than LEV for that protein [1]. If the SV2A protein was a relevant mechanism, BRV would be associated with an even higher risk of developing PAEs as compared with LEV. Conversely, the different effects on AMPA receptors can be a likely explanation for the different psychotropic effects of the two drugs [13,14]. Among all AEDs, those with AMPA antagonist properties, such as topiramate, zonisamide [15], and more recently, perampanel [16], have shown to be more frequently associated with PAEs [17]. Interestingly enough, while LEV has shown to be also an AMPA antagonist [13], BRV has no effect on glutamate neurotransmission [14]. A controlled study comparing directly LEV with BRV will be able to clarify if BRV is better tolerated than LEV.

The safety of the direct switch from LEV to BRV is another relevant finding of our case series. Even though in a small number of subjects, we observed no seizure deterioration, and there was no difference in the rates of reported adverse events in patients who underwent the overnight switch compared with those who underwent cross-titration or sequential titration. This is in keeping with previous reports suggesting that an overnight switch is safe and well tolerated [12,18]. However, our case series is the first in patients with psychiatric comorbidities.

Finally, in our case series, a very small number of patients were prescribed BRV off-label for drug-resistant generalized epilepsies. The scientific rationale for that was based on a previous Phase III study which included a subgroup of patients with generalized epilepsies [19]. None of our patients had a significant improvement on BRV, but none of them had deterioration either, further confirming that BRV is not associated with seizure deterioration in patients with generalized epilepsies. Studies investigating the potential role of BRV in patients with generalized syndromes are needed.

Limitations of this report should be noted. First, the retrospective nature and the very small sample size make our case series an anecdotal report. However, it provides detailed information on the use and outcome of BRV in patients with drug-resistant epilepsy and psychiatric comorbidities, a subgroup of patients that may be often challenging for many epileptologists.

Disclosure

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References

- [1] Russo E, Citraro R, Mula M. The preclinical discovery and development of brivaracetam for the treatment of focal epilepsy. *Expert Opin Drug Discovery* 2017;12:1169–78. <https://doi.org/10.1080/17460441.2017.1366985>.
- [2] Chen Z, Lusicic A, O'Brien TJ, Velakoulis D, Adams SJ, Kwan P. Psychotic disorders induced by antiepileptic drugs in people with epilepsy. *Brain* 2016;139:2668–78. <https://doi.org/10.1093/brain/aww196>.
- [3] Mula M, Sander JW. Negative effects of antiepileptic drugs on mood in patients with epilepsy. *Drug Saf* 2007;30:555–67.
- [4] Mula M. Epilepsy and psychiatric comorbidities: drug selection. *Curr Treat Options Neurol* 2017;19:44. <https://doi.org/10.1007/s11940-017-0483-0>.
- [5] Mula M, Hesdorffer DC, Trimble M, Sander JW. The role of titration schedule of topiramate for the development of depression in patients with epilepsy. *Epilepsia* 2009;50:1072–6. <https://doi.org/10.1111/j.1528-1167.2008.01799.x>.
- [6] Mula M, Trimble MR, Sander JW. Are psychiatric adverse events of antiepileptic drugs a unique entity? A study on topiramate and levetiracetam. *Epilepsia* 2007;48:2322–6. <https://doi.org/10.1111/j.1528-1167.2007.01262.x>.
- [7] Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. *Lancet* 2012;380:1180–92. [https://doi.org/10.1016/S0140-6736\(12\)61455-X](https://doi.org/10.1016/S0140-6736(12)61455-X).
- [8] Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. *Epilepsia* 2007;48:2336–44. <https://doi.org/10.1111/j.1528-1167.2007.01222.x>.
- [9] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;51:1069–77. <https://doi.org/10.1111/j.1528-1167.2009.02397.x>.
- [10] Toledo M, Whitesides J, Schiemann J, Johnson ME, Eckhardt K, McDonough B, et al. Safety, tolerability, and seizure control during long-term treatment with adjunctive brivaracetam for partial-onset seizures. *Epilepsia* 2016;57:1139–51. <https://doi.org/10.1111/epi.13416>.
- [11] Lattanzi S, Cagnetti C, Foschi N, Provinciali L, Silvestrini M. Brivaracetam add-on for refractory focal epilepsy: a systematic review and meta-analysis. *Neurology* 2016;86:1344–52. <https://doi.org/10.1212/WNL.0000000000002545>.
- [12] Yates SL, Fakhoury T, Liang W, Eckhardt K, Borghs S, D'Souza J. An open-label, prospective, exploratory study of patients with epilepsy switching from levetiracetam to brivaracetam. *Epilepsy Behav* 2015;52:165–8. <https://doi.org/10.1016/j.yebeh.2015.09.005>.
- [13] Carunchio I, Pieri M, Ciotti MT, Albo F, Zona C. Modulation of AMPA receptors in cultured cortical neurons induced by the antiepileptic drug levetiracetam. *Epilepsia* 2007;48:654–62 doi:EPI973 [pii] <https://doi.org/10.1111/j.1528-1167.2006.00973.x>.
- [14] Niespodziany I, Rigo J-M, Moonen G, Matagne A, Klitgaard H, Wolff C. Brivaracetam does not modulate ionotropic channels activated by glutamate, γ -aminobutyric acid, and glycine in hippocampal neurons. *Epilepsia* 2017;58:e157–61. <https://doi.org/10.1111/epi.13890>.
- [15] Perucca P, Mula M. Antiepileptic drug effects on mood and behavior: molecular targets. *Epilepsy Behav* 2013;26:440–9. <https://doi.org/10.1016/j.yebeh.2012.09.018>.
- [16] Ceolin L, Bortolotto ZA, Bannister N, Collingridge GL, Lodge D, Volianskis A. A novel anti-epileptic agent, perampanel, selectively inhibits AMPA receptor-mediated synaptic transmission in the hippocampus. *Neurochem Int* 2012. <https://doi.org/10.1016/j.neuint.2012.02.035>.
- [17] Brodie MJ, Besag F, Ettinger AB, Mula M, Gobbi G, Comai S, et al. Epilepsy, antiepileptic drugs, and aggression: an evidence-based review. *Pharmacol Rev* 2016;68:563–602. <https://doi.org/10.1124/pr.115.012021>.
- [18] Steinig I, von Podewils F, Möddel G, Bauer S, Klein KM, Paule E, et al. Postmarketing experience with brivaracetam in the treatment of epilepsies: a multicenter cohort study from Germany. *Epilepsia* 2017. <https://doi.org/10.1111/epi.13768>.
- [19] Kwan P, Trinka E, Van Paesschen W, Rektor I, Johnson ME, Lu S. Adjunctive brivaracetam for uncontrolled focal and generalized epilepsies: results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial. *Epilepsia* 2014;55:38–46. <https://doi.org/10.1111/epi.12391>.