

## Brivaracetam in Status Epilepticus: A Systematic Review

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### ABSTRACT

**Background:** Status epilepticus (SE) is a neurological emergency that carries a high morbidity and mortality. Although treatment of benzodiazepine-refractory SE has conventionally been intravenous phenytoin, it has several limitations including risk of infusion-site reactions, cardiac and haemodynamic compromise necessitating close monitoring during infusion, multiple drug interactions secondary to enzyme induction, and it can exacerbate certain seizure types including myoclonus and absence seizures. Brivaracetam (BRV), a novel, high affinity synaptic vesicle protein 2A (SV2A) ligand, has a more favourable side-effect profile, is easier to administer and has fewer drug interactions, making it an attractive alternative to phenytoin in SE.

**Aim:** A systematic review was performed to examine the evidence for the use of BRV in SE.

**Methods:** PubMed, EMBASE and Medline databases were searched in October 2018 using the search terms: status epilepticus and Brivaracetam. Articles were included provided they were original research articles published in the English language and examined the use of BRV in SE (convulsive and non-convulsive types) in adult patients.

**Results:** Only 3 studies met the inclusion criteria. Two were multi-centre retrospective cohort studies and the other was a retrospective case series. Interpretation was profoundly limited by the small number of participants (total  $n = 20$ ), the absence of controls, and was complicated by the fact that BRV was often used when multiple other anti-epileptic drugs (AEDs) had reportedly failed. BRV was noted to be most effective in terminating SE when administered at an early stage. No serious adverse drug reactions were noted during treatment in SE.

**Conclusions:** BRV can safely be used in both convulsive and non-convulsive SE, though randomised-controlled trials are required before conclusions can be drawn about its comparative efficacy with current conventional AED treatments.

### Keywords

Status epilepticus, Brivaracetam, Anti-epileptic drugs.

### Introduction

Status epilepticus (SE) is a neurological emergency that carries a high morbidity and mortality if not promptly and aggressively treated [1,2]. It is characterised by excessively synchronised neuronal firing that mediate epileptiform discharges, which drive the pathophysiological activation of neural plasticity at multiple spatial scales. These plasticity mechanisms operate at the molecular, cellular, synaptic and network levels, which serve to bolster hyper-excitable epileptic neural networks through a self-perpetuating positive feedback loop as a seizure progresses [3].

This is accompanied by a failure of the usual mechanisms that operate to terminate a seizure, leading to prolongation of seizure activity [4]. With increasing duration of seizure activity, inhibitory GABAergic synaptic transmission declines and excitatory NMDA-mediated synaptic currents increase [5]. This primes the neural circuitry into a 'run away' hyper-excitable state that becomes increasingly difficult to terminate the longer a seizure persists. Thus, SE requires early treatment if one is to reduce the probability of progression to refractory and super-refractory states [6].

Despite representing an important neurological condition presenting to the emergency department, the evidence underpinning the recommended treatments, particularly in benzodiazepine-

refractory cases, is surprisingly limited – the evidence continues to dwindle with refractory and super-refractory SE [7].

Although intravenous phenytoin (and its prodrug form, fosphenytoin) has traditionally been the drug of choice in benzodiazepine-refractory SE [8], it has several limitations. Intravenous infusion carries a risk of infusion-site reactions (e.g. purple glove syndrome), arrhythmia and hypotension, which necessitates close cardiac and blood pressure monitoring, and as a hepatic enzyme inducer, it can enhance the metabolism of many drugs including other anti-epileptic drugs (AEDs). Furthermore, phenytoin can exacerbate other seizure types including myoclonus and absence seizures. This calls for a need of alternative AED treatments in SE.

Brivaracetam (BRV) is a novel synaptic vesicle glycoprotein 2A (SV2A) ligand and a chemical analog of levetiracetam (LEV). Importantly, it is a safe drug with a favourable side-effect profile, is easier to administer and has minimal drug interactions [9]. The aim of this article is to systematically review the evidence for

intravenous BRV in SE in adults.

## Methods

PubMed, EMBASE and Medline databases were searched in October 2018 using the search terms: Status epilepticus and Brivaracetam. Articles were included provided they were original research articles published in the English language and examined the use of BRV in SE (convulsive and non-convulsive types) in adult patients.

## Results

A total of 3 studies met the inclusion criteria [10-12]. 2 were multi-centre retrospective cohort studies and 1 was a retrospective case series. No randomised-controlled trials (RCTs) were identified. A total of 20 patients with both convulsive and various forms of non-convulsive SE were treated with BRV. Efficacy varied from 0% to 57% response to IV BRV in the termination of SE, typically within 48 hours. Patients were more likely to respond the earlier they received treatment with IV BRV and less likely if they were in super-refractory SE (Table 1).

Authors	Study design	N	Age	Primary outcome	Other outcome measures and doses
Strzelczyk et al. 2017	Multi-centre retrospective cohort	11 (5F, 6M) GTCSE: 3 NCSE with coma: 6 Simple-partial SE: 1 Complex-partial SE: 1	Median 64 years (range 34-85)	SE ceased in 3/11 (27%) within 24 hrs of BRV  (8 had RSE, 3 had SRSE)	Median SE duration before BRV given: 5 days (range 1-29 days)  Median no. of previous AEDs used prior to BRV: 4 (range 1-8)  Median dose of BRV was 100mg (range 50-400mg) titrated to a daily median dose of 200mg (range 100-400mg)  No serious ADRs seen during BRV treatment.
Kalss et al. 2018	Single-centre retrospective case series	7 (6F, 1M)  GTCSE: 1 Myoclonic SE: 1 EPC: 2 NCSE with coma: 1 Aphasic status: 1 Aura continua: 1	Median 68 years (range 29-79)	- 4/7 (57%) responded to BRV with cessation of SE within 48hours  (These 4/7 patients all had early stage SE)	Median SE duration before BRV given: 10.5 hours (range 0.5 hours to 105 days)  Median no. of previous AEDs used prior to BRV: 4 (range 2-11)  Median loading dose of BRV: 100mg IV over 15 mins (range 50-200mg), titrated up to a median dose of 100mg/day (range 100-300mg)  No serious ADRs seen during BRV treatment.
Strzelczyk et al. 2018	Multi-centre retrospective cohort	2 females with absence SE (total n=61 in the study but only 2 had SE)	Mean age 29.8 years in entire study	0% response	200-300mg BRV was administered intravenously as a bolus – well-tolerated but no response was achieved.

**Table 1:** Outline of results from this systematic review. Key - ADR (Adverse drug reaction), BRV (Brivaracetam), EPC (epilepsia partialis continua), GTCSE (generalised tonic-clonic status epilepticus), NCSE (non-convulsive status epilepticus), RSE (refractory status epilepticus), SRSE (super-refractory status epilepticus).

## Discussion

Despite representing an important neurological emergency, the evidence underpinning the management of SE, particularly in benzodiazepine-refractory cases, is surprisingly limited [13].

Intravenous phenytoin, has traditionally been the AED of choice in benzodiazepine-refractory SE since the 1970s [13]. However, it is associated with multiple drawbacks including infusion-site reactions such as purple-glove syndrome, haemodynamic and cardiac compromise necessitating close monitoring during infusion, it induces the metabolism of many drugs and can exacerbate various seizure types including myoclonus and absences. Furthermore, patients placed on maintenance phenytoin

therapy during or immediately after resolution of SE often later require a switch to alternative AEDs that are better tolerated in the long-term, and commonly prescribed in current clinical practice, making phenytoin an impractical choice. Thus, consideration should be made for replacing phenytoin with other AEDs that have more favourable pharmacokinetics and side-effect profiles, as second-line treatment for SE.

A recent systematic review of randomised-controlled trials (RCTs) comparing intravenous phenytoin versus levetiracetam (LEV) in benzodiazepine-refractory SE has shown that these 2 AEDs have similar efficacies in seizure termination and similar functional outcomes at hospital discharge [14]. However, only 3 RCTs met

the inclusion criteria, each with relatively small n numbers, which precluded a conclusive evaluation of the data. Despite the extant limited evidence base, LEV is frequently preferred for SE [15]. Another AED, belonging to the same class of SV2A binders as LEV, is BRV, and may be even more favourable given its greater lipophilicity permitting more rapid penetration of the blood brain barrier [12].

A previous multi-centre retrospective cohort study has shown that BRV is safe and well-tolerated with a 75.8% retention rate at 6 months [9]. It also had a favourable side effect profile and although behavioural adverse events were amongst the most frequent drug reactions, these seemed to be less significant than LEV. Given that BRV is a novel agent, receiving FDA approval for partial-onset seizures in 2017, it is perhaps not surprising that the evidence for its utility in SE is even more limited than LEV. In this review, only 3 uncontrolled trials and no RCTs were identified. The studies demonstrated overall that BRV is safe for SE but no definitive conclusions can be drawn regarding its efficacy given the lack of 'n' numbers, the absence of control data and combined with the fact that BRV was typically given after multiple AEDs were used for refractory and super-refractory SE - the latter makes it difficult to disentangle the therapeutic effects of BRV from other concurrently prescribed AEDs.

In conclusion, there is a need for robustly powered RCTs comparing the clinical efficacy of BRV with other AEDs if one is to consider the routine use of this agent as an alternative to current conventional treatments.

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