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SYSTEMATIC REVIEW

Intravenous Brivaracetam in the Treatment of Status Epilepticus: A Systematic Review

Francesco Brigo[1,2] · **Simona Lattanzi**[3] · **Raffaele Nardone**[1,4] · **Eugen Trinka**[4,5]

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Abstract

Background Brivaracetam is a high-affinity synaptic vesicle glycoprotein 2A ligand with high brain permeability and rapid onset of action. These properties make brivaracetam potentially an ideal compound in the emergency setting.

Objective The objective of our study was to review the evidence about the clinical efficacy and tolerability of intravenous brivaracetam in the treatment of status epilepticus.

Methods We systematically searched MEDLINE, EMBASE, Google Scholar, ClinicalTrials.gov, and conference proceedings to identify studies evaluating intravenous brivaracetam as treatment for status epilepticus of any type in patients of any age. Searches were conducted on 3 December, 2018.

Results Seven studies were included (37 patients; aged 22–85 years; 21 were female). The type and etiology of status epilepticus varied across studies. The number of drugs used prior to brivaracetam to treat status epilepticus ranged from 1 to 8. The time from status epilepticus onset to brivaracetam administration ranged from 0.5 h to 105 days. The initial brivaracetam dose ranged from 50 to 400 mg. In case series, the proportion of patients achieving clinical status epilepticus cessation when brivaracetam was administered as the last drug varied from 27 to 50%; in case reports, all patients had status epilepticus cessation. The time from brivaracetam administration to status epilepticus cessation ranged from 15 min to 94 h. No serious adverse effects were reported.

Conclusions The available data suggested that brivaracetam can be a safe treatment option in patients with status epilepticus. The current evidence is however hampered by several confounding factors, and controlled studies are warranted to define the actual benefit of brivaracetam for the treatment of status epilepticus.

1 Introduction

Status epilepticus (SE) is a life-threatening condition and medical emergency associated with long-term consequences, including "neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures" [1], and a risk of mortality around 20% [2] increasing up to 33% in patients with impaired consciousness [3]. It is currently defined as a condition "resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally, prolonged seizures" [1].

The pharmacological management of SE follows a stepwise approach. Fast-acting benzodiazepines are administered as first-line treatments, leading to SE cessation in about 60–70% of cases [4–6]. In benzodiazepine-resistant cases, an intravenous (IV) administration of antiepileptic drugs (AEDs) is required to control SE and prevent or minimize the risk of negative long-term systemic or neuronal consequences, particularly in the case of convulsive SE [4, 5]. The

Francesco Brigo and Simona Lattanzi contributed equally.

✉ Francesco Brigo
dr.francescobrigo@gmail.com

1 Division of Neurology, "Franz Tappeiner" Hospital, Merano, Bolzano, Italy

2 Department of Neuroscience, Biomedicine and Movement Science, University of Verona, Piazzale L.A. Scuro, 10, 37134 Verona, Italy

3 Department of Experimental and Clinical Medicine, Neurological Clinic, Marche Polytechnic University, Ancona, Italy

4 Department of Neurology, Christian Doppler University Hospital, Paracelsus Medical University, Salzburg, Austria

5 Institute of Public Health, Medical Decision Making and Health Technology Assessment, University for Health Sciences, Medical Informatics and Technology, UMIT, Hall in Tyrol, Austria

Key Points

Preclinical studies have demonstrated that brivaracetam has high brain permeability and rapid onset of action; these properties suggest that brivaracetam could have a relevant role in the treatment of status epilepticus

In this systematic review, we assessed the evidence available so far on the clinical efficacy and tolerability of intravenous brivaracetam in the treatment of status epilepticus

Included studies were small and of marked clinical and methodological heterogeneity, comprising patients with different types and etiologies of status epilepticus. The proportion of patients achieving clinical status cessation when brivaracetam was administered as the last drug varied considerably across studies, and no serious adverse effect was observed

The available data on the clinical use of brivaracetam for the treatment of status epilepticus are very sparse and of low quality, hampered by clinical and methodological heterogeneity, and several confounding factors

Further observational (large case series and prospective registries) and controlled studies are needed to draw more robust conclusions on the role of brivaracetam for the treatment of status epilepticus

AEDs commonly used as second-line treatments for SE are phenytoin, phenobarbital, valproate, levetiracetam (LEV), and lacosamide [4, 5, 7]. If generalized tonic–clonic (convulsive) SE persists despite administration of IV AEDs, anesthetic therapy with all its complications is recommended.

Brivaracetam (BRV) is a high-affinity synaptic vesicle glycoprotein 2A ligand that is currently licensed as a treatment for focal-onset seizures in patients aged ≥ 4 years with epilepsy as monotherapy or adjunctive therapy [8]. After oral administration, BRV is rapidly and completely absorbed; it has low ($< 20\%$) plasma protein binding and a linear and predictable pharmacokinetic profile [9, 10]; furthermore, it carries minimal risks of drug–drug interactions [11].

Although structurally related to LEV, BRV has higher brain permeability, faster brain synaptic vesicle glycoprotein 2A occupancy, and more rapid onset of action [12, 13]. These properties make IV BRV potentially an ideal compound in the emergency setting, particularly in the treatment of SE. Although BRV is currently not labeled to treat SE, preclinical studies have been encouraging and showed efficacy in animal models of SE [12, 14]. The aim of our study was to systematically review the evidence about the clinical efficacy and tolerability of IV BRV in the treatment of SE.

2 Methods

The results of the present systematic review were reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. The review protocol was not previously registered.

We included any study evaluating IV BRV as treatment for SE of any type in patients of any age, irrespective of definition of SE adopted and neurological outcomes assessed.

The following electronic databases and data sources were systematically searched using the following search strategy: Brivaracetam AND "status epilepticus":

1. MEDLINE (January 1966–3 December, 2018), accessed through PubMed;
2. EMBASE;
3. Google Scholar;
4. ClinicalTrials.gov (available at: https://clinicaltrials.gov/);
5. Opengrey.eu (available at: www.opengrey.eu).

To minimize publication bias, we also searched the conference proceedings of international congresses by the International League Against Epilepsy and the American Epilepsy Society from 2016 onwards. All searches were conducted on 3 December, 2018. All resulting titles and abstracts were evaluated, and any relevant article was considered. No language restrictions were adopted. Retrieved articles were independently assessed for inclusion by two review authors (FB, RN); any disagreement was resolved through discussion.

The following data were independently extracted by two review authors (FB, RN) for any included study: main study author and date of publication; type of study; total number, age, and sex of participants; type and etiology of SE; previous or concomitant drugs, including order of administration and maximal dosage; dosage of BRV (initial dose, titration interval, maximal dose); use of BRV as last medication; number of drugs administered prior to BRV to treat SE; time from SE onset to BRV administration; number of patients achieving SE cessation when BRV was administered as the last drug; time from BRV administration to SE cessation (only for responders); neurological outcomes; occurrence and/or type of adverse effects. Limitations of included studies were discussed narratively. We did not plan

the quantitative synthesis of data as we expected to find great clinical and methodological heterogeneity between studies.

3 Results

A total of 326 records was identified (14 MEDLINE; 83 EMBASE; 227 Google Scholar; 0 ClinicalTrials.gov; 0 Opengrey.eu; 1 abstract proceedings of international congresses of the International League Against Epilepsy; 1 abstract proceedings of international congresses of the American Epilepsy Society). After removal of duplicates and reading title and abstracts, seven studies were eventually included [16–22] (Fig. 1).

Overall, 37 patients (21 were female) with ages ranging from 22 to 85 years were included. Characteristics of the included studies and participants are summarized in Table 1. There was a great heterogeneity in the type and etiology of SE across studies. Details on BRV administration and efficacy/tolerability outcomes are reported in Table 2. The number of drugs used prior to BRV to treat SE ranged from one to eight. The time from SE onset to BRV administration ranged from 0.5 h to 105 days. The initial BRV dose ranged from 50 to 400 mg. The proportion of patients achieving clinical SE cessation when BRV was administered as the last drug varied from 27 to 50%. In case reports, all patients achieved SE cessation. The time from BRV administration to SE cessation ranged from 15 min to 94 h. No serious adverse effects were reported.

For six responders in whom BRV was used as the last medication, individual patient data were available; in these patients (age: 61 ± 25 years; maximal median BRV dose: 200 mg, range 100–400 mg), the median time from BRV administration to SE cessation was 15 h (range 15 min–27 h) [18, 21]. In a case series not reporting individual data, the median time from BRV given as the last AED (numbers of prior AEDs: 1–6) to SE cessation was 22 h (range 5–96 h) [22]. In this study, responders (seven patients) received a significantly greater median loading dosage per body weight compared with non-responders (3.3 mg/kg vs. 1.5 mg/kg; $p = 0.02$); all responders had loading doses above 1.9 mg/kg [22].

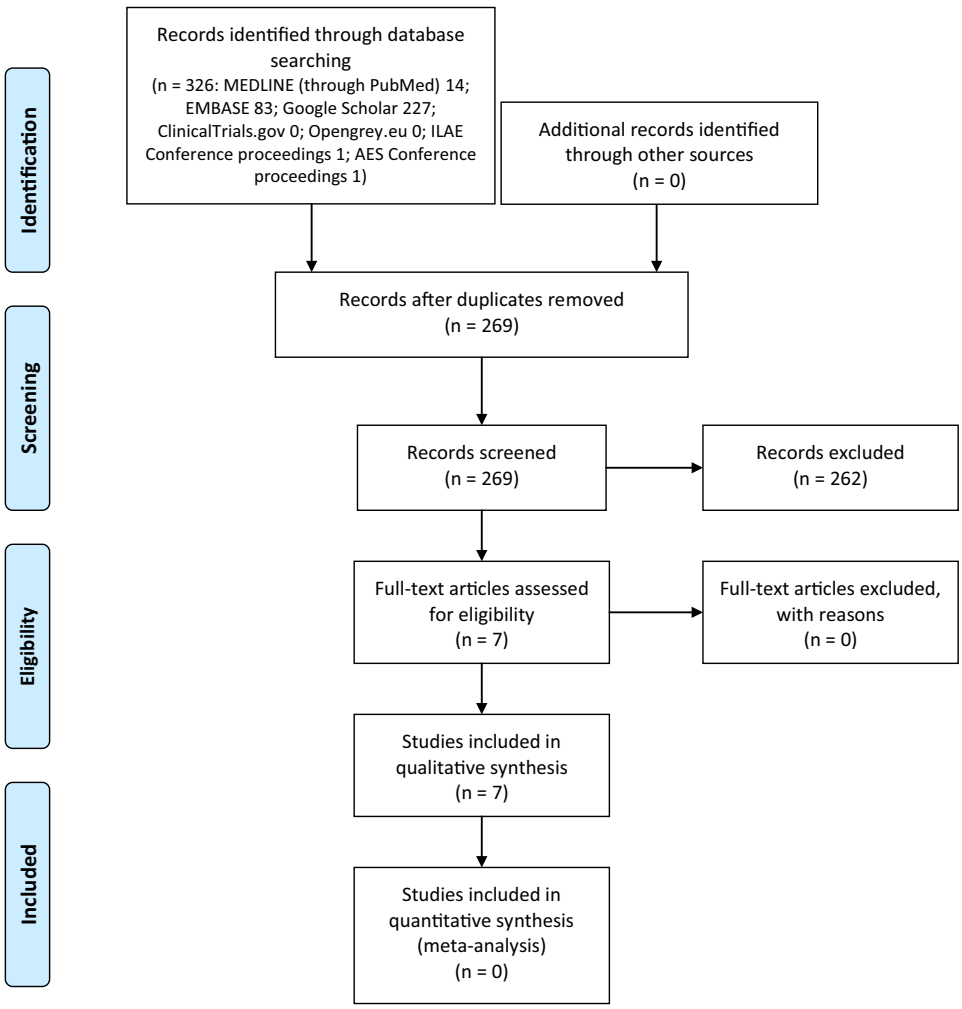

Fig. 1 Study inclusion flow diagram

Table 1 Study design, clinical characteristics of patients, and the type and etiology of status epilepticus (SE)

Study, year	Type of study	Number of patients	Age, years	Sex	Type of SE	Etiology of SE
Beier et al. (2016) [16]	Case report (unpublished)	1	58	M	GTCS subsequently developing into focal NCSE with coma	Unknown, concomitant glioblastoma multiforme (previous surgery, with radio- and chemotherapy; no tumor manifestation on MRI in right temporal lobe, the EEG focus of NCSE)
Fleming et al. (2017) [17]	Case report (unpublished)	1	65	F	GTCS subsequently developing into NCSE with coma	Posterior reversible encephalopathy syndrome
Strzelczyk et al. (2017) [18]	Bicenter retrospective chart review (published)	11	34	M	NCSE dyscognitive	Structural epilepsy remote ischemic
			54	M	NCSE dyscognitive	Structural epilepsy due to glioblastoma WHO IV
			54	M	GTCSE	Remote traumatic brain injury
			64	F	NCSE dyscognitive	Posterior reversible encephalopathy syndrome
			67	M	GTCSE	Glioblastoma WHO IV
			75	F	Focal motor SE	Structural epilepsy remote ischemic
			80	F	NCSE dyscognitive	Subarachnoid hemorrhage
			85	F	NCSE dyscognitive	Remote intracerebral hemorrhage
			52	F	NCSE with impaired consciousness	Structural epilepsy remote ischemic
			58	M	GTCSE	Remote subdural hemorrhage
			70	M	NCSE dyscognitive	Unknown, concomitant Alzheimer's disease
Strzelczyk et al. (2018) [19]	Multicenter retrospective cohort study (published)	2	28	F	Typical absence SE	Idiopathic generalized epilepsy (syndrome not further specified)
			22	F	Typical absence SE	Idiopathic generalized epilepsy (syndrome not further specified)
Manacheril et al. (2018) [20]	Case report (unpublished)	1	46	M	Focal motor SE	Stroke-like migraine attacks after radiation therapy (SMART) syndrome
Kalss et al. (2018) [21]	Single-center retrospective chart review (published)	7	32	F	NCSE with coma	Hypoxia
			79	M	NCSE without coma	Cerebrovascular
			75	F	NCSE without coma	Cerebrovascular
			68	F	Epilepsia partialis continua	Mitochondrial disorder
			30	F	GTCSE	Lissencephaly, microgyria, hippocampal sclerosis
			76	F	Myoclonic SE with coma	CNS infection
			29	F	Epilepsia partialis continua	Hypomelanosis of Ito
Aicua-Rapun et al. (2019) [22]	Single-center retrospective chart review (published)	14	61 (range 33–80)	F:M = 7:7	Focal ($n = 9$, 64%), convulsive SE ($n = 4$, 29%), non-convulsive SE in coma ($n = 1$, 7%)	NR

CNS central nervous system, *EEG* electroencephalogram, *F* female, *GTCSE* generalized tonic–clonic status epilepticus, *M* male, *MRI* magnetic resonance imaging, *NCSE* non-convulsive status epilepticus, *NR* not explicitly reported, *WHO* World Health Organization

4 Discussion

In this systematic review, we identified and critically appraised the currently available evidence on the use of IV BRV for the treatment of SE in a real-world clinical setting. The efficacy in case series varied considerably with cessation rates ranging from 27 to 50%. No adverse events have been reported, suggesting that BRV can be safely administered

to patients presenting with SE of different types and etiologies. The wide range of efficacy observed across the studies can find different explanations. The response rate of 100% may reflect publication bias, i.e., the higher likelihood of studies with positive results to be submitted and eventually published compared to studies with negative results [23]. To take into account and minimize this risk, we extended the searches to the gray literature looking for abstracts published in conference proceedings, but not yet published as full-length reports. At the same time, however, study results reported only as abstracts are inevitably less complete or preliminary compared with those published in final full-length articles. This could hamper the opportunity to establish a straight causal correlation between the intervention and clinical response. More specifically, it is not always possible to ascertain whether changes in co-medications were made, and details on the use of simultaneous or sequential drugs were not always reported.

The small number of patients may have increased the imprecision of results, and the great clinical heterogeneity of the included patients and the different dosages administered may account for the wide clinical response following BRV administration. The lack of information on the type and etiology of SE, both major determinants of treatment response [3, 24], as well as comorbidities prevented us from analyzing the contribution of these factors to the overall efficacy of BRV. Furthermore, the time from SE onset to BRV administration was extremely wide, ranging from 0.5 h to 105 days, and in many cases BRV was given in patients with super-refractory SE and after several attempts (up to eight) with other antiepileptic or anesthetic drugs. In these patients, BRV was probably used to treat SE associated with severe underlying brain dysfunction. The type and the etiology of SE were extremely heterogeneous across included studies, further limiting the robustness of any conclusions on the clinical role of BRV in the treatment of this condition.

The IV BRV doses used to replace oral therapy (100 mg BRV intravenously) were unlikely to represent a loading dosage enough to control SE in most patients [22]. In this regard, a recent study assessed the correlation between BRV exposure and clinical response. Interestingly, patients achieving SE cessation after being administered BRV as the last AED received a significantly greater median loading dosage per body weight compared with non-responders, and a minimum loading dose of 2 mg/kg has been proposed to be safe and likely advisable in the treatment of SE in adults [22]. The benefit of a further increase in loading doses was not investigated, and it is, hence, unclear whether IV BRV shows a ceiling effect in terms of response, similar to that demonstrated with the use of LCM at loading doses higher than 9 mg/kg [25].

Owing to high lipophilicity, BRV crosses the blood–brain barrier rapidly and has a tissue distribution similar to that of fast-acting benzodiazepines [26]. Remarkably, BRV has an entry half-time faster than 1 min, with a barely detectable distribution phase, and reaches its maximal brain concentration within 10 min after IV administration [12]. In animal models, BRV has been also shown to have a faster onset of anticonvulsant activity than LEV [12] and a supra-addictive efficacy with diazepam to control SE [14, 27].

However, the limited available data prevent us from drawing definitive conclusions about the onset of antiepileptic activity of BRV and comparative response with other AEDs. In the six patients in whom BRV was used as the last medication and for whom individual data were reported, the time from BRV administration to SE cessation ranged from 15 to 27 h. Although these figures might confirm the rapid onset of antiepileptic action for BRV, in a case series not reporting individual details, the median time from BRV given as the last AED to SE cessation (seven patients) was longer (22 h; range 5–96 h) [22].

The very low amount of clinical data on BRV in SE prevents us making a comparison with LEV. Although LEV is being increasingly used as a second-line treatment for SE [28], it has also been tested as first-line treatment for generalized convulsive SE in a prehospital randomized controlled trial aimed at determining the efficacy of adding intravenous LEV (2.5 g) to clonazepam (1 mg) [29]. This study did not demonstrate an additional benefit of adding LEV to clonazepam compared to clonazepam treatment alone in the prehospital control of SE (74% vs. 84%, respectively; percentage difference − 10.3%, 95% confidence interval − 24.0 to 3.4). However, it is "unlikely that the added benefit of LEV was adequately assessed in this trial, as any effect was likely overshadowed by the high success rate of clonazepam" [30]. Furthermore, the duration of observation (SE cessation was assessed at 15 min of drug injection) was probably not long enough to fully detect the antiepileptic activity of LEV.

The current evidence on BRV in SE is not enough to justify its use as a first-line drug, although preclinical data have provided promising results of a faster onset of anticonvulsant activity than LEV. If further studies will provide robust evidence showing a fast onset of antiepileptic activity for BRV, its use as a first-line treatment for SE, as a benzodiazepine substitute, could be considered. However, more data need to be collected, also considering that the large multicenter prospective registry, SENSE (Sustained Effort Network for treatment of Status Epilepticus), demonstrated that treatment failure is higher if AEDs are used as first-line treatment instead of benzodiazepines [31].

Table 2 Details of brivaracetam (BRV) treatment in included studies

Study, year	Patient (in studies providing individual data)	Previous or concomitant drugs in order of administration (maximal dosage)	BRV dose	BRV used as last medication	Number of drugs administered prior to BRV to treat SE	Time from SE onset to BRV administration	Cessation of SE, number of patients (%)	Time from BRV administration to SE cessation (only for responders)	Neurological outcome	Adverse effects
Beier et al. (2016) [16]	1	PHT and LEV (before admission); DZP (10 mg); LEV (load); LCM (400 mg); BRV	200 mg	Yes		3 NR	Yes	NR	Patient fully awake and conscious	NR
Fleming et al. (2017) [17]	1	fPHT; LCM; LEV; MDZ; PRO; KET (order of administration and maximal dosage NR)	NR	Yes	6 (switch from LEV to BRV)	NR	Yes	NR	Seizure freedom	NR
Strzelczyk et al. (2017) [18]	1	LEV (before admission; 2000 mg/d); LEV (4000 mg/d); LCM (600 mg/d); TPM (400 mg/d); PER (12 mg/d); BRV (300 mg/d); VPA (1600 mg/d)	Maximal dose 300 mg (initial dose 150 mg; titration interval 150 mg/d)	No	4 (switch from LEV to BRV; VPA administered after BRV)	16 d	No	–	mRS score at discharge: 4	No serious adverse effects
	2	LEV (before admission; 2000 mg/d); CBZ (before admission; 400 mg/d); MDZ (7.5 mg/d); BRV (200 mg/d); LCM (200 mg/d)	Maximal dose 200 mg (initial dose 100 mg; titration interval 100 mg/d)	No	1 (switch from LEV to BRV; LCM administered after BRV)	1 d	No	–	mRS score at discharge: 3	No serious adverse effects
	3	LEV (3000 mg/d); MDZ (812.5 mg/d); BRV (400 mg/d); LCM (400 mg/d); TPM (300 mg/d); LZP (3 mg/d)	Maximal dose 400 mg (initial dose 400 mg)	No	2 (co-administration with LEV within 1 h; LCM, TPM and MDZ administered after BRV)	1 d	No	–	mRS score at discharge: 0	No serious adverse effects
	4	LEV (2000 mg/d); MDZ (7.5 mg/d); LCM (400 mg/d); BRV (300 mg/d); VPA (1600 mg/d)	Maximal dose 400 mg (initial dose 300 mg; titration interval 100 mg/d)	No	3 (switch from LEV to BRV; VPA administered after BRV)	1 d	No	–	mRS score at discharge: 5	No serious adverse effects
	5	DZP (15 mg/d); LEV (2000 mg/d); VPA (1600 mg/d); LZP (2 mg/d); LCM (400 mg/d); MDZ (5 mg/d); BRV (400 mg/d)	Maximal dose 400 mg (initial dose 400 mg)	Yes	6 (co-administration with LEV within 1 h)	1 d	Yes	15 min (time from BRV administration to EEG resolution)[a]	mRS score at discharge: 5	No serious adverse effects

Table 2 (continued)

Study, year	Patient (in studies providing individual data)	Previous or concomitant drugs in order of administration (maximal dosage)	BRV dose	BRV used as last medication	Number of drugs administered prior to BRV to treat SE	Time from SE onset to BRV administration	Cessation of SE, number of patients (%)	Time from BRV administration to SE cessation (only for responders)	Neurological outcome	Adverse effects
	6	LEV (before admission; 2000 mg/d); LEV (3000 mg/d); LCM (600 mg/d); BRV (100 mg/d)	Maximal dose 100 mg (initial dose 50 mg; titration interval 50 mg/d)	Yes	2 (switch from LEV to BRV)	3 d	Yes	24 h (time from BRV administration to EEG resolution)[b]	mRS score at discharge: 2	No serious adverse effects
	7	MDZ (10 mg/d); LEV (4000 mg/d); LCM (400 mg/d); TPM (600 mg/d); BRV (200 mg/d); VPA (1600 mg/d)	Maximal dose 200 mg (initial dose 100 mg; titration interval 100 mg/d)	No	4 (switch from LEV to BRV)	5 d	No	–	mRS score at discharge: 6	No serious adverse effects
	8	LEV (4000 mg/d); VPA (3600 mg/d); LZP (6 mg/d); LCM (400 mg/d); BRV (100 mg/d)	Maximal dose 200 mg (initial dose 50 mg; titration interval 50 mg/d)	Yes	4 (switch from LEV to BRV)	9 d	Yes	24 h (time from BRV administration to EEG resolution)[b]	mRS score at discharge: 5	No serious adverse effects
	9	LEV (before admission; 2000 mg/d); LZP (6 mg/d); LEV (4000 mg/d); VPA (2400 mg/d); PHT (250 mg/d); PRO anesthesia > 24 h; PB (350 mg/d); thiopental anesthesia > 24 h; BRV (200 mg/d); LCM (500 mg/d)	Maximal dose 200 mg (initial dose 100 mg; titration interval 100 mg/d)	No	8 (switch from LEV to BRV; LCM administered after BRV)	6 d	No	–	mRS score at discharge: 5	No serious adverse effects
	10	LEV (4000 mg/d); LZP (8 mg/d); LCM (400 mg/d); MDZ (15 mg/d); PRO anesthesia > 24 h; MDZ anesthesia > 24 h; KET anesthesia > 24 h; TPM (600 mg/d); BRV (200 mg/d); PER (812 mg/d); PHT (1000 mg/d)	Maximal dose 200 mg (initial dose 100 mg; titration interval 100 mg/d)	No	8 (switch from LEV to BRV; PER and PHT administered after BRV)	10 d	No	–	mRS score at discharge: 5	No serious adverse effects

Table 2 (continued)

Study, year	Patient (in studies providing individual data)	Previous or concomitant drugs in order of administration (maximal dosage)	BRV dose	BRV used as last medication	Number of drugs administered prior to BRV to treat SE	Time from SE onset to BRV administration	Cessation of SE, number of patients (%)	Time from BRV administration to SE cessation (only for responders)	Neurological outcome	Adverse effects
	11	LEV (4000 mg/d); VPA (2400 mg/d); PHT (800 mg/d); LZP (3 mg/d); thiopental anesthesia > 48 h; PB (300 mg/d); LCM (600 mg/d); PRO anesthesia > 48 h; BRV (400 mg/d); CBZ (2100 mg/d); TPM (600 mg/d); OXC (1800 mg/d)	Maximal dose 400 mg (initial dose 200 mg; titration interval 200 mg/d)	No	8 (switch from LEV to BRV; CBZ, TPM and OXC administered after BRV)	29 d	No	–	mRS score at discharge: 5	No serious adverse effects
Strzelczyk et al. (2018) [19]	1[c]	LZP (4 mg/d); BRV (300 mg); VPA (1600 mg/d); LCM (400 mg/d)	Maximal dose 300 mg (initial dose 300 mg)	No	1 (VPA and LCM administered after BRV)	NR (< 1 d)	Yes	–	Cessation of SE	NR
	2[c]	MDZ (810 mg/d); BRV (200 mg/d); VPA (100 mg/d); LZP (2 mg/d)	Maximal dose 200 mg (initial dose 200 mg)	No	1 (VPA and LZP administered after BRV)	NR (< 1 d)	Yes	–	Cessation of SE	NR
Manacheril et al. (2018) [20]	1[c]	BRV (200 mg/d); VPA (1000 mg/d); vigabatrin (3000 mg/d); TPM (400 mg/d); LEV (3000 mg/d); LCM (200 mg/d) [order of administration NR]	Maximal dose 200 mg (initial dose and titration interval NR)	Unclear	NR	NR	Yes	NR	Asymptomatic	NR
Kalss et al. (2018) [21]	1	LZP; LEV; rivotril; PRO; VPA; LCM; MDZ; PHT; BRV; magnesium; piracetam. Before admission: none	Loading dose: 200 mg; maximal dose: 200 mg	No		8 12 d	No	–	GOS: 3	None regarding cardiorespiratory function
	2 [c]	LZP; LEV; LCM; BRV; VPA. Before admission: none	Loading dose: 100 mg; maximal dose: 100 mg	No		3 3 d	No	–	GOS: 5	None regarding cardiorespiratory function
	3	LCM; LZP; VPA; BRV; PHT. Before admission: LEV; VPA; PER	Loading dose: 50 mg; maximal dose: 200 mg	No		3 5 d	No	–	GOS: 4; immediate EEG improvement	None regarding cardiorespiratory function

Table 2 (continued)

Study, year	Patient (in studies providing individual data)	Previous or concomitant drugs in order of administration (maximal dosage)	BRV dose	BRV used as last medication	Number of drugs administered prior to BRV to treat SE	Time from SE onset to BRV administration	Cessation of SE, number of patients (%)	Time from BRV administration to SE cessation (only for responders)	Neurological outcome	Adverse effects
	4	LZP; LEV; LCM; BRV; PRO; TPM. Before admission: none	Loading dose: 100 mg; maximal dose: 300 mg	No		3 105 d	No	–	GOS: 3	None regarding cardiorespiratory function
	5	DZP; LZP; BRV. Before admission: LCM; LEV	Loading dose: 100 mg; maximal dose: 100 mg	Yes		2 10.5 h	Yes	27 h	GOS: 3; immediate EEG improvement	None regarding cardiorespiratory function
	6	LZP; BRV. Before admission: BRV; OXC	Loading dose: 100 mg; maximal dose: 200 mg	Yes		1 2 h	Yes	6 h	GOS: 3	None regarding cardiorespiratory function
	7	LZP; BRV. Before admission: VPA; primidone; BRV; rufinamide	Loading dose: 50 mg; maximal dose: 200 mg	Yes		1 0.5 h	Yes	0.5 h	GOS: 3; immediate EEG improvement	None regarding cardiorespiratory function
Aicua-Rapun et al. (2019) [22]	14 (all patients)	NR	Mean loading dose: 171.4 mg; median loading dose 200 mg. Mean maintenance dose: 207.1 mg; median maintenance dose 200 mg		From 1 to 6	Median 73 h (range 3–144)	7 (50%)		NR	No adverse events reported
	7 (responders)	NR	Median loading weight adjusted dose: 3.3 mg/kg	Yes	From 1 to 6	Median 87 h (range 31–137.5)	7 (100%)	Median 22 h (range 5–94)	NR	No adverse events reported
	7 (non-responders)	NR	Median loading weight adjusted dose: 1.5 mg/kg	NR	From 1 to 6	Median 22 h (range 3–144)	0		NR	No adverse events reported

AEDs antiepileptic drugs, *CBZ* carbamazepine, *d* day, *DZP* diazepam, *EEG* electroencephalogram, *fPHT* fosphenytoin, *GOS* Glasgow Outcome Score, *h* hour, *KET* ketamine, *LCM* lacosamide, *LEV* levetiracetam, *LZP* lorazepam, *MDZ* midazolam, *min* minutes, *mRS* modified Rankin Scale, *NR* not explicitly reported, *OXC* oxcarbazepine, *PB* phenobarbital, *PER* perampanel, *PHT* phenytoin, *PRO* propofol, *pts* patients, *SE* status epilepticus, *TPM* topiramate, *VPA* valproic acid

[a]Activity attenuation and subsequent resolution of SE was observed directly on EEG following BRV administration

[b]BRV was the last AED to be added, and no SE was observed on EEG within the following 24 h

[c]BRV was not the terminating drug

5 Conclusions

The information on the use of IV BRV in the treatment of SE is currently scarce and of low quality. It is based only on a few case reports and small case series and, therefore, hampered by several confounding factors and a high risk of biases. The evidence available so far does not support the use of BRV for the treatment of SE, unless more clinical data are prospectively collected in observational studies (large case series or registries). Hence, further controlled prospective studies in clinically homogeneous and larger cohorts are warranted to explore the efficacy and tolerability of IV BRV for the treatment of SE and to investigate whether higher loading doses can be more efficacious. Based on pharmacological properties and promising preclinical data, more clinical information should be also gathered on the use of BRV administered as second-line or even as first-line treatment for SE, as a benzodiazepine substitute, and the possible synergistic interactions with other antiepileptic agents.

Compliance with Ethical Standards

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Conflict of interest Francesco Brigo has acted as a paid consultant to Eisai and LivaNova, and received travel support from Eisai. Eugen Trinka has acted as a paid consultant to Eisai, EVER Neuro Pharma, Biogen Idec, Medtronics, Bial, and UCB and has received speakers' honoraria from Bial, Eisai, Boehringer Ingelheim, Biogen, Newbridge, Novartis, and UCB Pharma in the past 3 years. Eugen Trinka has received research funding from UCB Pharma, Biogen, Novartis, Bayer, Eisai, Red Bull, Merck, the European Union, FWF Österreichischer Fond zur Wissenschaftsförderung, and Bundesministerium für Wissenschaft und Forschung. Eugen Trinka is also part of the investigators planning the ESET Trial and a member of the Task Force on Classification of Status Epilepticus of the International League Against Epilepsy. Simona Lattanzi and Raffaele Nardone have no conflicts of interest that are directly relevant to the content of this article.

Ethical Approval This is a systematic review of the literature, and not an original research study involving human participants and/or animals.

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