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REVIEW

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Recent advances in the pharmacotherapy of epilepsy: brivaracetam and perampanel as broad-spectrum antiseizure drugs for the treatment of epilepsies and status epilepticus

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ABSTRACT

Introduction: Antiseizure drugs (ASDs) play a central and crucial role in the treatment of epilepsy patients, as the majority require anticonvulsant treatment for an extended period of time. Since up to 30% of patients are refractory to medical treatment, new therapeutic options are necessary. Perampanel (PER) and brivaracetam (BRV) are the latest approved ASDs that may be considered in a variety of epilepsy syndromes. PER has a distinct and selective mode of action on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and is licensed for use in focal and generalized epilepsies. BRV is a derivative of levetiracetam but exhibits a 20-fold higher affinity and a faster brain entry time as a synaptic vesicle glycoprotein 2A (SV2A) ligand.

Areas covered: This article reviews the advances in the epileptic treatment and provides a comparison of PER and BRV. Both drugs have shown comparable results in randomized controlled trials, and both are well tolerated.

Expert opinion: PER and BRV have the potential to perform as important, broad-spectrum ASDs with significant market shares. BRV's intravenous formulation and fast penetration into the brain and PER's unique mode of action will result in the more frequent use of both drugs in status epilepticus.

1. Introduction

Epilepsy is a chronic neurological disorder with the clinical hallmark of recurrent, mostly unpredictable seizures [1]. Affecting approximately 50 million people worldwide (prevalence: 0.5%), epilepsy represents a major burden for patients themselves as well as for their caregivers and relatives [2–6]. During the last few decades, the dissemination of specialized epilepsy centers as well as improvements in both epilepsy surgery and basic diagnostic methods (e.g. magnetic resonance imaging) have enhanced the availability of therapeutic options for patients with epilepsy [7–9]. However, the regular oral intake of antiseizure drugs (ASDs; synonymous for anticonvulsants; also called antiepileptic drugs or AEDs) still represents the standard therapy worldwide despite the number of available ASDs being limited, especially in view of the restricted approval of several drugs for only one of the major epilepsy types like focal epilepsy (FE) or genetic (formerly idiopathic) generalized epilepsy (GGE). In the last decade, there was also a trend towards the introduction of ASDs with a narrow indication such as Dravet syndrome or Lennox–Gastaut syndrome [10–12]. Moreover, substance-specific side effects or contraindications often reduce the number of feasible ASDs in individual cases (e.g. valproate for women of reproductive age). In FE, approximately 50% of

patients reach sustained seizure freedom with a first and another 20% to 25% with the second or third ASD, respectively. The remaining 25% to 30% of patients are classified as having drug-refractory epilepsy (DRE) with only a poor chance of seizure freedom of approximately 5% with every additional ASD attempted [13,14]. Especially for this subgroup of patients with epilepsy (PWE), the approval of new ASDs offers a chance for a reduction in seizure frequency or even the achievement of seizure freedom, but also other PWE may profit from newer substances that boast less interactions with other drugs or fewer side effects. During the last few years, especially brivaracetam (BRV) and perampanel (PER) were approved with high expectations on efficacy and tolerability, and their use and benefit have controversially been discussed [15,16].

The aim of this narrative review is to summarize the current knowledge on efficacy, safety, and tolerability of BRV and PER with a focus on postmarketing studies.

2. Methods

To identify relevant studies that evaluated the use of BRV and PER in epilepsy and SE, we performed a systematic literature search in electronic databases using a combined search strategy including the following keywords: brivaracetam, perampanel, epilepsy, seizure, status epilepticus in combination with

Article highlights

- Up to 30% of patients are refractory to medical treatment for epilepsy meaning new therapeutic options are necessary.
- As second available SV2A receptor antagonist, brivaracetam is a well-tolerated, safe and efficient alternative to levetiracetam, especially in patients with behavioral side effects.
- As AMPA receptor antagonist, perampanel is an efficient, safe and well-tolerated antiseizure drug with a unique mode of action.
- Based on their individual mode of action, use of brivaracetam and perampanel in daily practice will increase.
- Brivaracetam and perampanel may be considered in refractory and super-refractory status epilepticus.

This box summarizes key points contained in the article.

Boolean operators. The search was performed using the PubMed gateway of the MEDLINE database, Cochrane Central Register of Controlled Trials, and the Excerpta Medica database in April and May 2019. In addition, the reference lists of all identified studies were checked for additional studies. Furthermore, review articles on BRV and PER were available [16–18]. Using a standardized assessment form on the study design, methodological framework, data sources and outcome previously defined parameters, e.g. efficacy, safety, and tolerability of the substance, were extracted from each publication and systematically reported. Overall, more than 100 publications were screened. For publications on the use of BRV and PER in epilepsy, a minimum number of 25 patients was set to increase the readability of the paper and the tables. Regarding the use of both drugs in SE no minimum number of enrolled patients was defined due to the limited availability of data. Only original publications containing data from randomized controlled trials (RCTs) and case series as well as relevant case reports were used for this narrative review.

3. Brivaracetam as an add-on therapy in focal and off-label therapy in generalized epilepsies

3.1. Drug profile, pharmacodynamics, and pharmacokinetics

BRV was developed by UCB (Union Chimique Belge, Brussels, Belgium) and approved in early 2016 in the European Union (EU) and the United States (US) as adjunctive (add-on) therapy for the treatment of partial-onset seizures with or without secondary generalization in adult and adolescent patients aged 16 years or older [19]. In 2018, the United States Food and Drug Administration (FDA) extended BRV's approval to monotherapy of focal seizures in patients aged four years and older. In the EU, only the age limit was lowered to four years without extending the approval to monotherapy. BRV is currently not approved for GGE or primary generalized seizures. BRV is subject to patent protection and only available under the trade name Briviact®, where the recommended dosage is between 25 and 100 mg twice daily for patients aged 16 years or older. In paediatric patients from 4 to 16 years of age the recommended dosage is based on body weight and ranges

between a minimum of 0.5 to 2.5 mg/kg and a maximum of 1mg/kg to 5mg/kg twice daily for patients weighing 11 to less than 20 kg and a minimum of 0.5 to 2 mg/kg and a maximum of 1mg/kg to 4mg/kg twice daily for those weighing 20 to less than 50 kg. For children and adolescents with a body weight over 50 kg recommended maintenance dosage is equal to those of adults with 25 to 100 mg twice daily [20]. BRV is available as 10 mg, 25 mg, 50 mg, 75 mg, or 100 mg film-coated tablets; a 10 mg/mL oral solution; and a 10 mg/mL solution for bolus injections or infusion [18]. BRV mainly acts as a ligand of the synaptic vesicle glycoprotein 2A (SV2A), which has been revealed as an important target for ASDs [21–27]. In comparison with the structurally related and well-established ASD levetiracetam (LEV), BRV has a higher lipophilicity and brain permeability and shows an 8.7- to 30-fold higher affinity to SV2A [23,25,28–34]. After oral application, BRV is rapidly absorbed with a modest first-pass effect and with low interindividual variability. Half-life is dose-independent at approximately eight to nine hours [25,35]. The pharmacokinetics of BRV are linear and dose-dependent, with a weak binding to plasma protein and a distribution volume that is close to total body water [36]. BRV is extensively metabolized by hepatic enzymes (mainly via CYP2C19) [36] and all of its metabolites are pharmacologically inactive [35,37]. Approximately 95% of the metabolites are eliminated through urine with an unchanged fraction of 8% to 11% [36,38]. Hepatic dysfunction increases the plasmatic half-life of BRV up to 17.4 h [35], while renal impairment not requiring dialysis has only modest effects on BRV clearance [39]. The simultaneous intake of carbamazepine (CBZ) can lead to decreased CBZ and BRV blood levels, while there might be an increase in CBZ-epoxide levels at the same time [25,40]. In addition, a decreased BRV plasma concentration upon treatment with phenobarbital (PB) and phenytoin has been described [38].

3.2. Clinical efficacy, safety, and tolerability

Six large-randomized controlled trials (RCTs) of different approval phases (II and III) using daily BRV doses of 5 to 200 mg in adult patients older than 16 years of age with focal-onset seizures revealed a greater-than-50% seizure reduction in 21.9% to 55.8% of all BRV-dosed cases. Taking only the finally recommended doses of 50 to 200 mg into account, a greater-than-50% seizure reduction was achieved in 26.8% to 55.8% of subjects. Treatment-emergent adverse events (TEAEs) were reported in 53.9% to 68.4%, with the most frequent symptoms being headache, somnolence, dizziness, and fatigue [41–46].

Further evidence on the efficacy, tolerability, and safety of BRV in clinical practice can be drawn from several postmarketing studies, which focus on the use of BRV in different patient subsets [47–55]. In 2017, a first retrospective multicenter analysis involving 262 patients aged five to 81 years was published by Steinig et al., revealing a responder rate of 41.2% after three and one of 40.5% after six months of treatment with 50 to 400 mg/d of BRV, respectively. TEAEs were reported by 37.8% of the subjects, including mostly sedation (16.0%), dizziness (11.8%), and nausea (9.1%) [52]. Two retrospective, single-center studies

analyzed BRV application in mixed cohorts of adolescents and adult patients with previous therapy-refractory focal and generalized epilepsies using daily doses of 50 to 200 mg/d. A decrease in seizure frequency of more than 50% was reported in 21.7% and 27.8% of the two groups, while TEAEs were reported in 24.0% and 36.6%, with dizziness, somnolence, ataxia, irritability, and depression being the most frequent [47,48]. Another retrospective analysis reported first evidence on the off-label use of BRV in children, adolescents, and adult patients with generalized epilepsies and daily intake of 25 to 150 mg of BRV. Here, a more-than-50% seizure reduction was observed in 36.0% and TEAEs occurred in 26.0% of patients, with sedation, irritability, and depression being the most frequent symptoms [49]. Efficacy and tolerability of 50–300 mg of BRV per day as off-label use in children and adolescents with focal epilepsy were analyzed by Schubert-Bast et al., who found a 50%-responder rate in 35.3% after six months and in 21.0% after one year of continuous BRV therapy. TEAEs were observed in 18.4% and comprised mostly symptoms of the central nervous system and behavioral abnormalities [51]. Moreover, the use of 25 to 100 mg of BRV daily in children, adolescents, and adult patients with epileptic encephalopathies was addressed, showing a more-than-50% seizure reduction in 45% of patients and a TEAE rate of 26.0%, with irritability, aggression, and sedation being frequently reported symptoms [50]. Efficacy and tolerability of 100–-200 mg/d of BRV in 33 patients aged 17 to 63 years with intellectual disability were analyzed by Andres et al., revealing a 19.0% responder rate. TEAEs occurred in 48.0% of subjects, including mostly behavioural changes (39.4%), ataxia (6.1%), and sedation (6.1%) [53]. Recently, another large retrospective multicenter study with 575 patients aged 16 years or older taking BRV 15 to 400 mg/d showed a responder rate of 39.7%, with an increase in seizure frequency reported by 12.6% of the study participants. The TEAE rate of 39.8% was described with somnolence (11.3%), irritability (6.6%), and dizziness (6.3%) being the most frequently reported symptoms [54].

Elsewhere, a large post-hoc analysis of the pivotal RTCs has been published that addresses different aspects of safety and tolerability or analyzing different subsets of patients according to their previous AED regime, epilepsy syndrome, or age [56–61]. For detailed information on the study design, population, efficacy, and tolerability results of the mentioned studies, please refer to Table 1.

4. Perampanel as add-on therapy in focal and generalized epilepsies

4.1. Drug profile, pharmacodynamics, and pharmacokinetics

PER was developed by Eisai Co., Ltd. (Tokyo, Japan) and approved in 2012 in the EU and US as adjunctive treatment for partial-onset seizures with or without secondary generalization in patients aged 12 years or older. In 2015, PER was additionally approved for the adjunctive treatment of primary generalized tonic-clonic seizures in patients with GGE from 12 years of age in the EU and US. In the meantime, the age limit in FE was lowered by the FDA to four years of age and older and the drug's use was simultaneously extended to monotherapy. PER is subject to patent protection and only available under the trade name Fycompa®, with the recommended dosage being between 2 and 12 mg once daily for children aged 12 years or older, as well as for adolescents and adults. PER is available as 2, 4, 6, 8, 10, and 12-mg tablets [62,63]. A 0.5 mg/mL suspension for oral intake was also recently developed. PER is the first selective, noncompetitive antagonist of ionotropic a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor for glutamate [64,65]. After oral intake, PER is rapidly absorbed without any relevant first-pass effect. Simultaneous food intake reduces the rate of absorption. PER's half-life is dose-independent at approximately 105 h, and the drug shows a linear pharmacokinetics profile and is extensively bound to plasma proteins. PER is extensively metabolized by hepatic enzymes (CYP3A4, CYP3A5) and is mainly excreted by feces (70%) but also via the urine [66,67]. The simultaneous intake of CBZ, lamotrigine (LTG), valproate (VPA), oxcarbazepine (OXC), phenytoin (PHT), and topiramate (TPM) may result in a decreased PER plasma concentration. Vice versa, PER increases markedly the plasma concentration of OXC by up to 35% [66,67].

4.2. Clinical efficacy, safety, and tolerability

First evidence for the efficacy, safety, and tolerability of PER was derived from four large RCTs leading to the approval of PER for its use as add-on therapy in patients with partial-onset seizures in patients aged 12 years or older [68,69] or 18 years or older [70]. Krauss et al. performed two dose-escalation studies in 153 and 48 patients, respectively, with daily PER doses ranging between 2 and 12 mg per day, ultimately finding 50%-responder rates of 30.7% and 39.5% and TEAE rates of 66.7% and 84.2%, with dizziness, headache, and somnolence as most reported symptoms [70]. Another study considering 8 and 12 mg of PER per day revealed 50%-responder rates of 37.6% and 36.1%, with 90.0% of enrolled patients reporting TEAEs – predominantly dizziness, somnolence, and headache [69]. The fourth RCT with 706 patients employed 2, 4, and 8 mg of PER daily, resulting in a greater-than-50% seizure reduction in 20.6%, 28.5%, and 34.9% of the cases dosed with each amount. Overall, 65.8% of subjects reported TEAEs, with dizziness, somnolence, and headache being the most frequent symptoms [68]. A long-term extension study of the mentioned dose-escalation studies conducted among patients with focal-onset seizures aged 18 years or older [70] with a total of 138 analyzed subjects revealed that 38.4% of the initially treated patients were still taking PER over a time period of up to four years. Here, a − 31.5% change in seizure frequency was revealed, with 93.5% of the patients reporting TEAEs during their treatment with PER. The most frequent symptoms mentioned were dizziness, headache, and somnolence [71].

Overall, three RCTs analyzed the use of PER in groups of patients aged 12 years or older with focal-onset seizures taking doses of 2, 4, 8, 10, or 12 mg of PER daily, revealing a more-than-50% seizure reduction in 33.3% to 59.0%, respectively, and a change in seizure frequency of −17.3% to 38.0%, depending on the individual dose of PER. TEAEs were reported in 76.5% to 86.4% of patients taking PER, including mostly dizziness, somnolence, headache of fatigue [72–74]. In addition, five extension studies in patients with partial-onset

Table 1. Overview on studies primarily addressing efficacy, safety and tolerability of brivaracetam as add-on treatment in patients with epilepsy.

Study layout	Study design		Epilepsy	Dosage (mg/d)	Efficacy > 50% seizure reduction (%)	TEAE rate (%)	Safety and tolerability Frequent neurological TEAE (%)
	Study population						
	n	age (y)					
RCTs and other pivotal studies							
French et al. [2010, 41] db, r, pc	208	16–65	POS	5 / 20 / 50	32.0 / 44.2 / 55.8	53.9	Headache (4.5) Somnolence (4.5) Dizziness (3.2)
van Paesschen et al. [2013, 42] db, r, pc	157	16–65	POS	50 / 150	39.6 / 33.3	67.6	Headache (11.4) Fatigue (9.5) Somnolence (7.6)
Biton et al. [2014, 44] db, r, pc	396	16–70	POS	5 / 20 / 50	21.9 / 23.2 / 32.7	75.2	Somnolence (15.1) Dizziness (14.1) Headache (10.1)
Kwan et al. [2014, 45] db, r, pc	480	16–70	FE, GGE	20–150	30.3	66.0	Headache (14.2) Somnolence (11.1) Dizziness (8.6)
Ryvlin et al. [2014, 43] db, r, pc	398	16–70	POS	20 / 50 / 100	27.3 / 26.8 / 36.0	60.7	Headache (13.8) Somnolence (7.4) Dizziness (5.7)
Klein et al. [2015, 46] db, r, pc	760	17–80	POS	100 / 200	38.9 / 37.8	68.4 / 66.8	Somnolence (18.1) Dizziness (12.3) Fatigue (9.5)
Postmarketing studies							
Steinhoff et al. [2017, 48] rs, sc	101	18–81	FE, GGE	50–400	27.8	36.6	Dizziness (15.8) Somnolence (9.9) Ataxia (5.0)
Steinig et al. [2017, 52] rs, mc	262	5–81	FE, GGE	50–200	$41.2_{3months}$ $40.5_{6months}$	37.8	Sedation (16.0) Dizziness (11.8) Nausea (9.1)
Hirsch et al. [2018, 47] rs, sc	46	11–70	FE, GGE	50–200	21.7	24.0	Irritability (6.5) Depression (6.5) Other (4.3)
Andres et al. [2018, 53] rs, mc Focus: patients with intellectual disability	33	17–63	FE, GGE	100–200	19.0	48.0	Behavioural changes (39.4) Ataxia (6.1) Sedation (6.1)
Schubert-Bast et al. [2018, 51] rs, mc Focus: children and adolescents	34	3–17	FE	50–300	$35.3_{6\,months}$ $21.0_{12\,months}$	18.4	CNS related (8.8) Behavioural (5.9) Other (5.9)
Strzelczyk et al. [2018, 49,52] rs, mc Focus: GGE	61	9–90	GGE	25–150	36.0	26.0	Sedation (9.8) Irritability (9.8) Depression (4.9)
Willems et al. [2018, 50] rs, mc Focus: epileptic encephalopathies	44	6–62	EE	25–100	45.0	16.0	Irritability (9.1) Aggression (6.8) Sedation (2.3)
Zahnert et al. [2018, 55] rs, sc	93	Mean: 43.9	FE	50–200	35.1	39.8	Irritability (7.5) Depression (7.5) Fatigue (7.5)
Villanueva et al. [2019, 54] rs, mc	575	≥ 16	FE	15–400	39.7	39.8	Somnolence (11.3) Irritability (6.6) Dizziness (6.3)
Post-hoc analysis and other studies							
Ben-Menachem et al. [2016, 60] Focus: efficacy, safety, tolerability	1.160	-	POS	50–200	-	68.0	Somnolence (15.2) Dizziness (11.2) Headache (9.6)
Brodie et a. [2016, 59] Focus: efficacy, safety, tolerability in older patients	32	≥ 65	POS	50 / 100 / 200	25.0 / 50.0 / 66.7	73.3	Headache (12.5) Paraesthesia (12.5) Somnolence (12.5)

(Continued)

Table 1. (Continued).

| | Study design | | | | | Efficacy | Safety and tolerability | |
| | Study layout | Study population | | Epilepsy | Dosage (mg/d) | > 50% seizure reduction (%) | TEAE rate (%) | Frequent neurological TEAE (%) |
		n	age (y)					
Kälviainen et al. [2016, 61]	Focus: efficacy, safety, tolerability in ULD	106	≥ 16	ULD	5–150	-	68.0–78.6	Headache (13.21–14.7) Somnolence (5.9–18.4) Myoclonus (5.9–18.4)
Moseley et al. [2016, 58]	Focus: efficacy, safety, tolerability	150	16–80	POS	5–200	-	39.4	Somnolence (12.6) Headache (11.0) Dizziness (8.3)
Arnold et al. [2018, 56]	Focus: conversion to BRV monotherapy	150	16–75	POS	50–200	-	73.3	Fatigue (10.0) Convulsion (9.3) Anxiety (8.7)
Benbadis et al. [2018, 57]	Focus: concomitant LTG or TPM	220$_{LTG}$ 122$_{TPM}$	16–80	POS	5–200	33.6$_{LTG}$ 35.5$_{TPM}$	68.7$_{LTG}$ 65.6$_{TPM}$	Somnolence (14.0/21.3) Dizziness (14.0/11.5) Fatigue (9.3/9.8)

db = double-blind, r = randomized, ra = retrospective analysis, mc = multicenter, sc = single-center, hc = historical controlled.
POS = partial onset seizures, GGE = genetic generalized epilepsy, EE = epileptic encephalopathies, ULD = Unverricht–Lundborg disease, TEAE: treatment-emergent adverse event, FE = focal epilepsy.

seizures aged 12 years or older that were previously enrolled in the initial RCTs before the approval of PER was published. Here, long-term responder rates of 58.0% to 62.7% after 92 to 104 weeks [75,76], 37.0% (mean duration of exposure: 195 weeks) [77], or 37.9% after 16 weeks [78] were reported. TEAEs rates in these extension studies were 72.5%, 87.4%, 91.3%, and 91.5%, with dizziness, somnolence, and headache being the most frequent symptoms. Another RCT analyzed the use of 2 to 8 mg of PER in patients with tonic-clonic seizures and genetic generalized epilepsies. Here, a responder rate of 64.2% and a TEAE rate of 82.7% were reported, with dizziness, fatigue, and headache as frequently observed symptoms [79].

Since PER's approval, more than 10 postmarketing studies have been published addressing efficacy, safety, and tolerability of PER in clinical practice [72,74,80–82]. The efficacy and tolerability of PER in children, adolescents, and adults were targeted by two retrospective analyses in patients aged eight to 12 years old or 12 to 18 years old using 2 to 8 mg or 2 to 12 mg, respectively, of PER per day. Here a more-than-50% reduction in seizure frequency was observed in 12.8% of the total patient population, including in 30.3% after three, 27.5% after six, and 34.7% after 12 months of treatment, while TEAEs were reported in 12.8% and 37.9% of the two age groups [80,81]. Moreover, a large multicenter observational study involving 2,396 patients of all age groups taking different doses of PER revealed a responder rate of 42.0% and a TEAE rate of 67.6% with dizziness (20.6%), behavioral AEs (19.1%), and somnolence (15.0%) as the most frequently reported symptoms. Two other retrospective multicenter studies addressed safety, efficacy and tolerability of PER in small children from 2 to 17 (n = 58) respectively, 6 to 18 (n = 62) years of age in pediatric patients with focal and generalized epilepsies. A 50% responder-rate of 31%, respectively, 50% was reported, TEAE rates were 30.6%, respectively, 48.0% with fatigue, behavioral changes, disturbance, dizziness, and sedation as most common symptoms [83,84].

Furthermore, a large post-hoc analysis of the pivotal RTCs published addressing different aspects of safety and tolerability, dose response, or concomitant enzyme–inducing AEDs (EAEDs) have been published [85–87]. For detailed information on the study design, population, efficacy, and tolerability results of the studies mentioned, please refer to Table 2.

5. Brivaracetam and perampanel as add-on therapy in status epilepticus

Status epilepticus is a life-threatening condition and a medical emergency that is associated with increased morbidity and mortality [88,89]. Treatment remains difficult if first- and second-line therapies fail in refractory SE (RSE) and even general anesthesia fails in super-refractory SE (SRSE) [90]. Due to the severity of illness and unfavorable outcomes, there is a critical need for new therapies to stop ongoing seizure activity [91].

There are only a few retrospective case reports, case series, and small studies available containing evidence for the off-label use of BRV [92–94] and PER [62,95–98] as add-on therapy in the treatment of RSE and SRSE.

The efficacy of intravenous BRV in RSE and SRSE was analyzed in three case series containing seven, 11, and 14 patients in the

Table 2. Overview on studies primarily addressing efficacy, safety, and tolerability of perampanel as add-on treatment in patients with epilepsy.

	Study design					Efficacy	Safety and tolerability	
		Study population				> 50% seizure reduction (%)	TEAE rate (%)	Frequent neurological TEAE (%)
	Study layout	n	age	Epilepsy	Dosage (mg/d)			
RCTs and other pivotal studies								
French et al. [2012, 69]	r, db, pc, mc	388	≥ 12	POS	8 12	37.6 36.1	90.0	Dizziness (37.8) Somnolence (24.1) Headache (14.2)
Krauss et al. [2012, 70]	r, db, pc, mc	153	18–70	POS	4	30.7	66.7	Dizziness (13.7) Headache (9.8) Somnolence (7.8)
Krauss et al. [2012, 70]	r, db, pc, mc, dose-escalation study	48	18–70	POS	2–12	39.5	84.2	Dizziness (57.9) Somnolence (31.6) Headache (18.4)
Krauss et al. [2012, 68]	r, db, pc, mc	706	≥ 12	POS	2 4 8	20.6 28.5 34.9	65.8	Dizziness (17.5) Somnolence (12.5) Headache (10.2)
Rektor et al. [2012, 71]	r, db, pc, mc extention study	138	18–70	POS	2–12	$-31.5_{change\ in\ SF}$	93.5	Dizziness (41.3) Headache (21.0) Somnolence (19.6)
post-marketing studies								
French et al. [2013, 72]	r, db, pc, mc	386	≥ 12	POS	8 12	33.3 33.9	86.4	Dizziness (40.0) Somnolence (15.2) Fatigue (14.8)
Krauss et al. [2013, 75]	r, db, pc, mc extension study	1.218	≥ 12	POS	2–12	$41.4_{week\ 14–26}$ $36.9_{week\ 40–52}$ $62.7_{week\ 92–104}$	87.4	Dizziness (43.9) Somnolence (20.2) Headache (16.7)
Krauss et al. [2014, 76]	db, r, mc, pc extension study	1.216	≥ 12	POS	2–12	$32–35_{week\ 1–13}$ $42–48_{week\ 14–26}$ $52_{week\ 27–39}$ $58_{week\ 92–104}$	91.3	Dizziness (46.8) Somnolence (21.2) Headache (18.3)
Biro et al. [2015, 83]	r, mc	58	2–17	FE, GGE; EE	-	31.0	48.0	Fatigue (27.6) Behavioural changes (24.1)
French et al. [2015, 79]	db, r, pc, mc	164	≥ 12	GGE	2–8	64.2%	82.7	Dizziness (32.1) Fatigue (14.8) Headache (12.3)
Montouris et al. [2015, 78]	r, db, pc, mc extension study	1.218	12–76	POS	2–12	37.9	91.5	Dizziness (47.5) Somnolence (22.4) Weight increase (10.5)
De Liso et al. [2016, 84]	r, mc	62	6–18	FE	2–12	50.0%	30.6	Irritability (11.3) Fatigue (11.3) Dizziness (9.7)
Lagae et al. [2016, 73]	db, r, pc, mc	85	12–17	POS	8–12	59.0	80.0	Dizziness (30.6) Somnolence (15.3) Headache (10.6)
Kanemura et al. [2018, 81]	r, sc	39	12–18	POS	2–12	12.8	12.8	-
Lin et al. [2018, 80]	r, mc	66	8–18	FE, GGE	2–8	$30.3_{3\ months}$ $37.5_{6\ months}$ $34.7_{12\ months}$	37.9	Irritability (10.6) Skin rash (10.6) Dizziness (9.1)
Nishida et al. [2018, 74]	db, r, mc, pc	710	≥ 12	POS	4 8 12	$-17.3_{change\ in\ SF}$ $-29.0_{change\ in\ SF}$ $-38.0_{change\ in\ SF}$	76.5	Dizziness (31.3) Somnolence (17.1) Nasopharyngitis (13.2)
Rohracher et al. [2018, 82]	rs, mc observational study	2396	-	FE, GGE	-	42.0	67.6	Dizziness (20.6) Behavioural (19.1) Somnolence (15.0)
Usui et al. [2018, 77]	db, r, mc, pc extension study	51	≥ 12	POS	2–12	37.0	72.5	Dizziness (37.3) Somnolence (31.4) Headache (5.9)
post-hoc analysis								
Steinhoff et al. [2013, 85]	Focus: safety and efficacy	1.478	≥ 12	POS	2 4 8 12	-28.5 35.3 35.0	77.0	Dizziness (28.1) Somnolence (14.5) Headache (11.4)
Kramer et al. [2014, 86]	Focus: dose-response	1.038	≥ 12	POS	8 12	37.2 42.9	77.0	Dizziness (28.1) Somnolence (14.5) Headache (11.4)
Gidal et al. [2015, 87]	Focus: concomitant EIAED	1.480	≥ 12	POS	2–12	-	79.2	Dizziness (22.2) Somnolence (15.7) Fatigue (11.0)

db = double-blind, r = randomized, ra = retrospective analysis, mc = multicenter, sc = single-center, hc = historical controlled.
POS = partial-onset seizures, GGE = genetic generalized epilepsy, EE = epileptic encephalopathies, ULD = Unverricht–Lundborg disease, TEAE: treatment-emergent adverse event, FE = focal epilepsy, SF = seizure frequency.

Table 3. Overview on the add-on use of intravenous brivaracetam in status epilepticus.

	study design			status epilepticus		therapy regimen			efficacy
		study population							
	layout	n	age (y)	type	severity	median no AEDs used before	loading dose (mg)	maintenance dose (mg/d)	responder rate
Strzelczyk et al. [2017, 93]	ra, mc	11	34–85	NCSE CSE	RSE SRSE	4	50–400	100–400	27%
Kalss et al. [2018, 92]	ra, sc	7	29–79	NCSE CSE	RSE	4	50–200	100–300	43%
Strzelczyk et al. [2018, 49]	ra, mc	2	23–38	ASE	Established SE	1	200–300	-	-
Aicua-Rapun et al. (2019)	ra, sc	14	33–80	NCSE CSE	RSE SRSE	5	100–200	200–300	50%

ra = retrospective analysis, sc = single-center, mc = multicenter, RSE = refractory status epilepticus, SRSE = super–refractory status epilepticus, ASE = absence status epilepticus, NCSE = nonconvulsive status epilepticus, CSE = convulsive status epilepticus, TEAE: treatment-emergent adverse event.

Table 4. Overview of the add-on use of oral perampanel in status epilepticus.

	study design			status epilepticus		therapy regimen			efficacy
		study population							
	layout	n	age (y)	type	severity	median no AEDs used before	loading dose (mg)	maintenance dose (mg/d)	responder rate
Redecker et al. [2015, 95]	ra, sc	9	57–82	EPC NCSE	RSE	6	2–6	-	22%
Rohracher et al. [2015, 62]	ra, sc	12	60–91	NCSE CSE	RSE	4	2–12	4–12	16%
Rohracher et al. [2018, 92]	ra, sc	30	18–91	NCSE CSE	RSE	4	2–32	12–20	17%
Ho et al. [2019, 98]	ra, mc	22	26–89	NCSE CSE	RSE SRSE	4	2–8	2–12	36%
Strzelczyk et al. [2019, 97]	ra, mc	52	19–91	NCSE CSE	RSE SRSE	5	2–24	4–24	37%

ra = retrospective analysis, sc = single-center, mc = multicenter, RSE = refractory status epilepticus, SRSE = super–refractory status epilepticus, NCSE = nonconvulsive status epilepticus, CSE = convulsive status epilepticus, EPC = epilepsia partialis continua.

age range of 23 to 85 years old. The loading-dose of BRV ranged between 50 and 400 mg and the maintenance dose was maintained at between a minimum of 100 mg and a maximum of 400 mg per day, while the responder rate, which was inconsistently defined based on clinical and/or electroencephalography (EEG) criteria, ranged between 27% and 50% [92–94]. The targeted dose of BRV in SE should be at 2 to 4 mg per kg body-weight [94]. Moreover, the use of BRV in two female patients with genetic generalized epilepsy suffering from absence status epilepticus has been published; however, BRV did not resolve SE in either patient [49].

The use of oral PER as add-on therapy in RSE and non-convulsive SE was first addressed in two case series involving nine and 12 patients between 57 and 91 years of age. The individual loading doses ranged between 2 and 12 mg and the maintenance doses were between 4 and 12 mg/d. A response to the introduction of PER was reported in 16% and 22% of the treated patients [62,95]. Moreover, three retrospective studies with 22, 30, and 52 patients aged between 18 and 91 years old (one of them including patients from a previously reported case series [62]) have been published. Here, a loading dose of between 2 and 32 mg of PER and a maintenance dose of 2 to 24 mg/d of PER were used. Responder rates of 17%, 36%, and 37% were reported based on different clinical and/or EEG criteria. For more details on the study design, population, and loading and maintenance doses of the mentioned studies, please refer to Table 3 for BRV and Table 4 for PER. Recently, a case report highlighting the efficacy of PER in three patients with RSE and

mitochondrial encephalopathy with lactic acidosis and stroke-like episodes–syndrome was revealed. Each patient received a different loading dose of PER of either 8, 16, or 12 mg and cessation of SE was observed in all cases at four to 8 h after administration [99].

6. Conclusion

Based on the large amount of studies underlining the efficacy, safety, and tolerability of the aforementioned two most recently approved drugs in the therapy of epilepsies with partial-onset seizures in adults and elderly patients, both BRV and PER may be ruled as effective and reliable broad-spectrum ASDs. Regarding the difference between high TEAE rates in the pivotal RCT studies compared to significantly lower TEAE rates in post-marketing analyses, the frequency of clinically important TEAE in daily practice seems to be comparable to other well-established ASDs, such as lacosamide, carbamazepine, oxcarbazepine or eslicarbazepine [100,101]. Moreover, their off-label use in several studies on genetic generalized epilepsies, epilepsy syndromes, or on the therapy of children and adolescents with epilepsy showed a tolerability and efficacy comparable to levels of other well-established ASDs. Due to their specific mode of action targeting SV2A or AMPA receptors, respectively, with high affinity, BRV and PER do not show any clinically relevant interactions with other ASDs, which makes them suitable substances for add-on therapies in patients with focal or generalized epilepsies [15,16,18,49,93].

In comparison with LEV, the up-to-30-fold increased affinity of BRV to its structural target and the faster brain entry time has to be weighted with an increased interaction rate due to its hepatic metabolization, possibly leading to a higher interaction potential [18]. Also, as compared with LEV, BRV seems to cause less behavioral TEAEs (e.g., depression, aggression, mania), making it a feasible substitute for patients who develop these side effects with LEV usage [52]. With a responder rate (>50% reduction in seizure frequency) of approximately 30%, the effectivity of both drugs BRV and PER does not rank behind that of other established drugs, such as lacosamide, topiramate, or eslicarbazepine [100–103]. There is only sparse evidence on the use of BRV and PER in SE. However, the use of BRV in SE has the advantage of an intravenous solution option being available, which enables a fast delivery of the medication combined with rapid penetration into the central nervous system, as recently shown in a positron-emission tomography study that revealed SV2A binding in healthy volunteers [27]. So far, however, the limited available data only show its use at later stages of SE rather reporting efficacy rates at the lower end. A reliable and comparable assessment of efficacy will only be possible if BRV is used as a second or third-line medication in SE. Data availability on the use of PER in SE is also limited, but the results of these studies are encouraging; however, the lack of availability of an intravenous solution makes its use less likely to occur during the early stages of SE.

7. Expert opinion

Based on the initial approval for the treatment of focal-onset seizures, extension to monotherapy, and lowering of the age limit to four years, both drugs will rapidly increase their market share. This and several publications on postmarketing experience show that epilepsy specialists consider BRV and PER as useful alternatives not only in patients with drug-refractory FE but also in genetic generalized epilepsies. In this indication, however, only PER in those patients from the age of 12 onwards is approved for the treatment of primary generalized tonic-clonic seizures. For the next few years, BRV and PER will likely remain as the only new broad-spectrum ASDs on the market, as is true with cannabidiol and fenfluramine, two ASDs that are in the process of approval for Dravet syndrome and Lennox–Gastaut syndrome. Cannabidiol and fenfluramine both have an orphan-drug designation and, due to anticipated high prices, these drugs will be probably not be used in a broad population of epilepsy patients.

The side-effect profiles of BRV and PER are comparable to those of other AEDs and include dizziness, somnolence, and psychiatric disorders. The latter may therefore restrict their use in patients with psychiatric comorbidity. At this time, long-term experience is still needed to exclude potentially severe late-occurring adverse events and to obtain data regarding their use and safety in pregnancy.

Application of BRV and PER in RSE and SRSE will probably increase due to their individual mode of action and as other newly developed options like brexanolone have failed in SE trials [104]. However, the questions remain as to whether a parallel administration of several ASDs with different mechanisms of action could positively influence the course of an RSE or SRSE and regarding which combination(s) would be the best choices. Neither of these questions can be answered with today's data. With the increased use of both drugs in SE, it is desirable that a trend will be discernible with respect to which patients and in which treatment contexts an application could improve patient outcomes and prognosis.

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