SYSTEMATIC REVIEW

Therapeutic Options for Patients with Refractory Status Epilepticus in Palliative Settings or with a Limitation of Life-Sustaining Therapies: A Systematic Review

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Abstract

Background Refractory status epilepticus (RSE) represents a serious medical condition requiring early and targeted therapy. Given the increasing number of elderly or multimorbid patients with a limitation of life-sustaining therapy (LOT) or within a palliative care setting (PCS), guidelines-oriented therapy escalation options for RSE have to be omitted frequently.

Objectives This systematic review sought to summarize the evidence for fourth-line antiseizure drugs (ASDs) and other minimally or non-invasive therapeutic options beyond guideline recommendations in patients with RSE to elaborate on possible treatment options for patients undergoing LOT or in a PCS.

Methods A systematic review of the literature in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, focusing on fourth-line ASDs or other minimally or non-invasive therapeutic options was performed in February and June 2020 using the MEDLINE, EMBASE and Cochrane databases. The search terminology was constructed using the name of the specific ASD or therapy option and the term 'status epilepticus' with the use of Boolean operators, e.g. "(brivaracetam) AND (status epilepticus)". The respective Medical Subject Headings (MeSH) and Emtree terms were used, if available.

Results There is currently no level 1, grade A evidence for the use of ASDs in RSE. The best evidence was found for the use of lacosamide and topiramate (level 3, grade C), followed by brivaracetam, perampanel (each level 4, grade D) and stiripentol, oxcarbazepine and zonisamide (each level 5, grade D). Regarding non-medicinal options, there is little evidence for the use of the ketogenic diet (level 4, grade D) and magnesium sulfate (level 5, grade D) in RSE. The broad use of immunomodulatory or immunosuppressive treatment options in the absence of a presumed autoimmune etiology cannot be recommended; however, if an autoimmune etiology is assumed, steroid pulse, intravenous immunoglobulins and plasma exchange/plasmapheresis should be considered (level 4, grade D). Even if several studies suggested that the use of neurosteroids (level 5, grade D) is beneficial in RSE, the current data situation indicates that there is formal evidence against it.

Conclusions RSE in patients undergoing LOT or in a PCS represents a challenge for modern clinicians and epileptologists. The evidence for the use of ASDs in RSE beyond that in current guidelines is low, but several effective and well-tolerated options are available that should be considered in this patient population. More so than in any other population, advance care planning, advance directives, and medical ethical aspects have to be considered carefully before and during therapy.

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Key Points

There is sustainable evidence for the efficacy of fourth-line antiseizure drugs (ASDs) in status epilepticus (SE) and refractory SE (RSE).

Lacosamide, topiramate, perampanel, brivaracetam, and stiripentol should be considered in patients with RSE in limited therapy settings.

Besides ASDs, the ketogenic diet can be a therapy option that must be individually evaluated for every case.

There is minor evidence for the use of magnesium sulfate in non-eclamptic SE as an additional therapeutic approach.

A central part of any medical therapeutic decision in RSE is the reflection of medical ethical aspects in the context of the patient's will.

1 Introduction

Status epilepticus (SE) is a frequent and potentially life-threatening medical condition that must be treated immediately to prevent further harm from befalling the affected patient. SE can not only manifest in patients with known epilepsy but can also have many other triggers, such as infection, brain damage, electrolyte imbalance, and auto-immune or paraneoplastic antibodies [1, 2]. According to German and other national and international clinical practice guidelines, benzodiazepines (BZDs) represent the first-line therapy in the treatment of SE. The International League Against Epilepsy defines all tonic–clonic seizures lasting for more than 5 min, as well as focal seizures with impaired consciousness or absence seizures lasting for more than 10 min, as SE [3]. An SE that lasts for more than 10 min despite adequately administered therapy with BZDs should be treated with intravenous antiseizure drugs (ASDs) such as levetiracetam (LEV), valproic acid (VPA), or (fos-)phenytoin (PHT) [4]. In the recently published ESETT trial, all three drugs showed similar efficacy profiles, at 47% (LEV), 45% (fosPHT), and 46% (VPA), in terminating an established SE, while having similar incidence rates of adverse events (AEs) [4]. If the combination of one BZD and one ASD fails, then criteria for a refractory SE (RSE) are met and further treatment in the intensive care unit (ICU), as well as the consequent use of anesthetic drugs together with the need for mechanical ventilation, are recommended for generalized tonic–clonic SE [5–8]. Failure to control SE with anesthetic

drugs defines a super-refractory SE (SRSE) that is associated with increased mortality, decreased quality of life, and poor chance of response to further therapeutics [2, 9–14]. Due to demographic changes such as an increasing number of elderly and multimorbid patients [15, 16], as well as the growing importance of self-determination for, in particular, severely ill patients within a palliative care setting (PCS) or with another limitation of life-sustaining therapy (LOT) [17], most of the recommended therapeutic options for RSE and SRSE fail due to invasiveness or the requirement of an ICU/IMC stay, invasive monitoring or mechanical ventilation [18, 19]. Moreover, based on the increasing implementation of advanced care planning (ACP), many patients have decided already in times of good health conditions or at the onset of a chronic or potentially life-threatening disease to waive specific medical treatment options [20]. However, many patients and their relatives or caregivers insist on a therapeutic attempt in spite of the given LOT or PCS, as SE per se does not always result in an additional permanent disability [21]. Moreover, many patients with acute or pre-existing relevant cardiopulmonary or hepatorenal conditions cannot be treated with several second- or third-line ASDs due to their high interaction potential (i.e. with phenobarbital [PB], PHT, or VPA), proarrhythmic effects (e.g. PHT), or contraindications to their use in combination with other drugs (e.g. enhanced VPA metabolism due to carbapenem antibiotics) [5, 19, 22].

This systematic review sought to summarize the evidence for fourth-line ASDs and other minimally or non-invasive therapeutic options beyond guideline recommendations in patients with RSE to elaborate on possible treatment options for patients undergoing LOT or in a PCS.

2 Methods

2.1 Characteristics of the Review

To evaluate the possible therapeutic options for patients undergoing ACP or LOT, or in a PCS, beyond the guideline recommendations, a systematic review of the literature was performed in February 2020 using the MEDLINE, EMBASE, and Cochrane databases, using the PubMed gateway, focusing on minimally or non-invasive treatment options that do not require invasive monitoring or admission to the ICU. Based on reviewers' recommendations, a second literature study was performed in June 2020 focusing on immunomodulatory and immunosuppressive treatment options. Studies with patients of all age ranges were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were closely followed; the PRISMA checklist for this review is available on request [23, 24]. The search terminology was

constructed using the name of the specific ASD or therapy option and the term 'status epilepticus' with the use of Boolean operators, e.g. "(brivaracetam) AND (status epilepticus)". The respective Medical Subject Headings (MeSH) and Emtree terms were used, if available. The protocol for this systematic review has not been previously registered on PROSPERO [25]. As other minimally or non-invasive therapeutic options, the intravenous application of magnesium sulfate ($MgSO_4$), neurosteroids (e.g. allopregnanolone), and the ketogenic diet (KD), as well as steroid pulse (SP), intravenous immunoglobulins (IVIGs) and plasma exchange/plasmapheresis (PLEX), were considered based on recent publications [1, 2]. No further filter was applied to avoid the falsification of the results, and two reviewers (LMW, AS) screened the identified articles for eligibility. Publications were defined as 'relevant' if the following criteria were met: (1) original publication; (2) human study; (3) at least one enrolled patient; and (4) sufficient data to enable a comparison with other publications. Reasons to exclude publications from this review included the unavailability of a version in English, French, German, Italian, or Spanish. Available reviews with a total of over 300 enrolled subjects for the use of a single ASD or other therapeutic options were used to cross-check the selected publications [26–41]. Processed data (e.g. number of subjects, age range, study design, characterization of SE, severity of SE, loading dose, maintenance dose, responder rate, rate of AEs in studies on ASDs) of the individual studies were manually transferred into a previously conceived assessment form. In addition, other aspects such as nutrition regimen, number of patients achieving ketosis (of those on KD), treatment days, relapse of seizures after the discontinuation of therapy ($MgSO_4$), treatment days, and titration and maintenance (if taking neurosteroids) doses were accessed. Regarding immunomodulatory and immunosuppressive therapies, treatment options and the specific response was recorded. Moreover, individual aspects of particular interest, and the strengths and weaknesses of each study, were assessed. Due to the use of processed data, cross-checking for double entries of single individuals was impossible and no additional post hoc subgroup analysis was performed. The risk of a specific bias was assessed for each publication; however, due to the low number of available publications with predominantly small numbers of enrolled patients, no studies were excluded, and major biases were discussed, except one study with previously proven fundamental statistical errors. The responder rate was defined as the primary outcome, while safety and tolerability (AEs) were defined as secondary outcomes for this study.

2.2 Level of Evidence

The well-established and internationally accepted Oxford classification scheme from the Oxford Centre for Evidence-Based Medicine (CEBM; March 2009) [42] was used to graduate the existing evidence based on the available quality and design of the published studies and reports in the following order.

(1) Randomized controlled trials (RCT) *or* meta-analyses of RCTs with homogenous results.
(2) Poorly designed RCTs, prospective cohort studies, *or* meta-analyses of level 2 studies.
(3) Retrospective cohort studies, case–control studies, *or* meta-analyses of level 3 studies.
(4) Case series.
(5) Case reports, expert opinions, *or* personal observations.

Based on the available amount, quality, and consistency of the available publications, the following different grades of recommendation can be concluded.

(A) Consistent level 1 studies.
(B) Consistent level 2 or 3 studies *or* extrapolations from level 1 studies.
(C) Level 4 studies *or* extrapolations from level 2 or 3 studies.
(D) Level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

In addition to the Oxford classification scheme, which focuses on the existing evidence, the Grading Recommendations Assessment, Development, and Evaluation (GRADE) scale was adopted to access the strength of recommendations [43]. The GRADE significance is subdivided into the following four quality levels.

(I) 'High', wherein we are very confident that the true effect lies close to that of the estimate of the effect.
(II) 'Moderate', wherein we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.
(III) 'Low', wherein our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
(IV) 'Very low', wherein we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

The displayed level of evidence and grade of recommendation for each ASD or therapeutic option represents the consensus of all authors of this publication.

2.3 Definitions and Terminology

Definitions and terminology for seizures, epilepsy, and SE used for this review follow the international recommendations of the International League against Epilepsy [3, 44, 45]. Due to the method-inherent character of this systematic review, no reappraisal of the reported responder or AE rates was performed, which means that all patients with a reported response or AE were counted without any further subcategorization. If AEs were not explicitly named or their absence was reported, AEs were classified as not available. Definitions and terms in relation to therapeutic restrictions, palliation, and end-of life care follow the current doctrines [20, 46] (please refer to the Infobox for more information).

Infobox

Advance Care Planning (ACP): ACP describes the process that enables individuals to plan their future healthcare by providing directions to caretakers, relatives, and healthcare professionals when the affected person is not in a position to make or communicate their own healthcare choices [20]

Limitation of Life-Sustaining Therapy (LOT): LOT is a therapy setting derived from decisions by individual ACPs that restrict the adoption of specific medical options in the case of deterioration in health status. Typical examples of a LOT are the renunciation of treatment in the intensive care unit, mechanical ventilation or intubation, organ replacement procedures, or resuscitation in the case of cardiac arrest [20]

Palliative Care Setting (PCS): PCS is a defined as a limited treatment regimen that focuses on treatment strategies for improving the quality of life of patients and their caregivers in patients with life-threatening illnesses and unfavorable prognoses through the prevention and relief of suffering [46]

2.4 Data Analysis and Reporting

All numbers with decimals were rounded to the nearest full number except those of dose recommendations in pediatric patients. No further data analysis or processing was performed for this systematic review.

3 Results

3.1 General Aspects

A total of 1481 publications were screened, resulting in the identification of 191 (13%) publications that were relevant to the topic of this systematic review. For more details on the PRISMA diagram, please refer to Fig. 1. Of these 191 publications, 62 (32%) focused on ASDs and 129 (68%) focused on other therapeutic options. Among fourth-line ASDs, the highest number of relevant publications was available for lacosamide (LCM; $n = 27$, 44%), followed by topiramate (TPM; $n = 15$, 24%), perampanel (PER; $n = 9$, 15%), brivaracetam (BRV; $n = 5$, 8%), stiripentol (STP; $n = 3$, 5%) and lamotrigine (LTG), oxcarbazepine (OXC) or zonisamide (ZNS; $n = 1$ each, 2%). Regarding other therapeutic options, most relevant publications reported on immunomodulatory and immunosuppressive therapies ($n = 72$, 65%), followed by the KD ($n = 30$, 23%), $MgSO_4$ ($n = 23$, 18%) and neurosteroids ($n = 4$, 3%).

3.2 Antiseizure Drugs (ASDs)

BRV is a novel third-generation ASD available in tablet, oral, and intravenous solution forms and is approved for monotherapy (US FDA) or add-on therapy (European Medicines Agency) in focal epilepsy (FE). BRV is a derivate of LEV, acting mainly as a ligand at the synaptic vesicle glycoprotein 2A (SV2A). In comparison with LEV, BRV has a tenfold increased affinity to its molecular target and boasts a lower potential for inducing psychobehavioral adverse effects [37, 47, 48]. BRV is not approved for use in SE; the evidence for its use is limited to five retrospective case series and reports offering a total of 77 adult cases with responder rates for convulsive SE (CSE) and non-convulsive SE (NCSE) of between 27 and 54%, as well as an acceptable tolerability profile [49–53]. The largest available retrospective multicenter cohort included 43 adult patients and reported a responder rate of 54% as well as good tolerability, with AEs observed in 14% of the enrolled subjects [50]. Two studies provided a subgroup analysis of a connection between responders and dosage showing a significant correlation of a response with a loading dose of 1.82–2.0 mg/kg body weight or greater [50, 53]. According to the current state of knowledge, a loading dose of 50–400 mg, considering the given minimum dose of approximately 2 mg/kg body weight and a maintenance dose of 100–400 mg/day, has been shown to be well tolerated and effective (Table 1b).

Carbamazepine (CBZ) is a second-generation ASD available in tablet and oral solution forms only, unfolding its anticonvulsive effect via voltage-gated sodium (Na^+) channels and being approved for both monotherapy and add-on
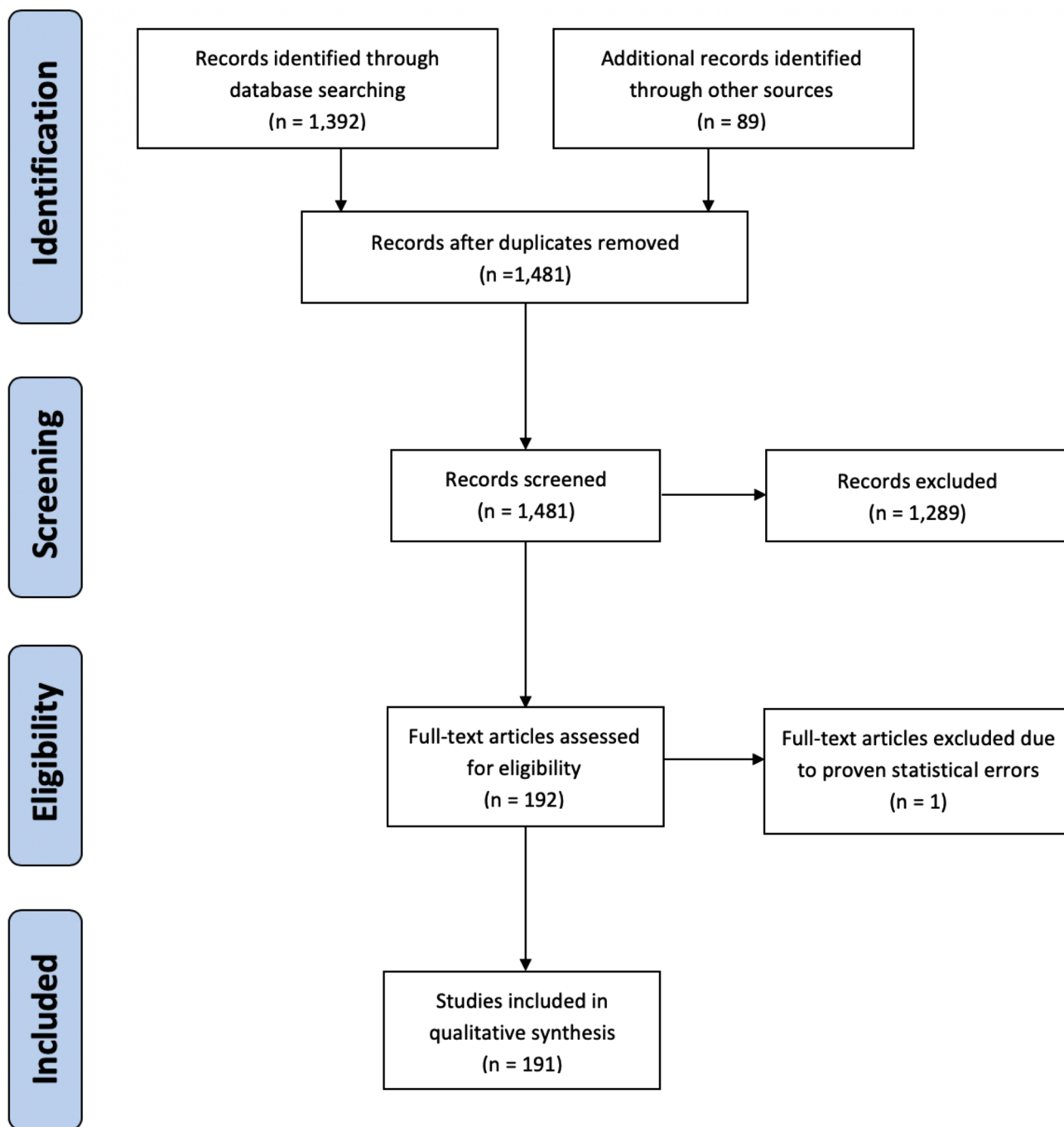
Fig. 1 PRISMA flow diagram. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

therapy in FE [54]. There is currently no evidence supporting the efficacy, safety, or tolerability of CBZ in SE.

Eslicarbazepine (ESL) is a third-generation ASD approved for monotherapy and add-on therapy for FE, and is available in an oral formulation with the same mechanism of action as that of OXC, i.e. the modulation of voltage-gated Na^+ channels [54]. There is currently no evidence supporting the efficacy, safety, or tolerability of ESL in SE.

LCM is a third-generation ASD available in tablet, oral, and intravenous forms and is approved for both monotherapy and add-on therapy in FE, which unfolds its effect by antagonism at voltage-gated Na^+ channels. LCM is currently not approved for use in SE. There are 20 retrospective case reports or series, as well as seven prospective studies, for a total of 862 pediatric and adult patients with CSE and NCSE, showing a responder rate ranging from 0 to 100%.

Table 1 Current evidence for the use of second- and third-line ASDs in refractory and super-refractory status epilepticus

	Study design			Status epilepticus		Therapy regimen		Outcome	
	Layout	Study population		Type	Severity	Loading dose (mg)	Maintenance dose (mg/day)	Response (%)	AEs (%)
		n	Age (years)						
(a) Lacosamide (LCM)									
Kellinghaus et al. (2011) [55]	rs, mc	39	18–90	CSE	SE, RSE	200–400	–	44	77
Albers et al. (2011) [56]	rs, sc	7	33–83	CSE	SE, RSE	400	400	100	–
Goodwin et al. (2011) [57]	rs, sc	9	47–89	CSE, NCSE	RSE	200	400	0	22
Höfler et al. (2011) [58]	rs, mc	31	22–95	CSE, NCSE	SE, RSE, SRSE	200–400	0–400	81	–
Koubeissi et al. (2011) [59]	rs, sc	4	53–79	NCSE	RSE	50–200	100–200	100	0
Rantsch et al. (2011) [60]	rs, sc	9	52–84	NCSE	RSE	50–100	–	20	–
Jain and Harvey (2011) [61]	rs, mc	31	12–17	CSE, NCSE	SE, RSE	50–200	0–400	75–100	4
Cherry et al. (2012) [62]	rs, sc	24	24–80	NCSE, CSE	RSE	100–400	300–400	38	31
Mnatsakanyan et al. (2012) [63]	rs, sc	10	16–90	NCSE	RSE	200–300	200–400	70	–
Belcastro et al. (2013) [64]	ps, sc	16	77 ± 7	NCSE	SE	400	400	50	-
Miró et al. (2013) [65]	ps, mc	34	22–86	CSE, NCSE	RSE	100–400	100–600	65	6
Santamarina et al. (2013) [66]	rs, sc	31	21- 85	CSE, NCSE	SE, RSE	200–600	400	85	13
Sutter et al. (2013) [67]	rs, sc	86	65 ± 15	CSE, NCSE	SE, RSE, SRSE	200	200	93	0
Legros et al. (2014) [68]	ps, cs	25	36–74	CSE, NCSE	SE, RSE	200–400	400	36	20
Kellinghaus et al. (2014) [69]	rs, sc	21	18–90	CSE, NCSE	RSE	200–800	200–800	33	–
Garcés et al. (2014) [70]	rs, mc	55	18–90	CSE, NCSE	SE, RSE	50–400	50–400	71	15
Grosso et al. (2014) [71]	rs, mc	11	3–16	CSE, NCSE	RSE	6.7–9.9[a]	8.8–13.9[a]	45	0
Poddar et al. (2016) [72]	rs, sc	9	0–16	CSE	SE, RSE	3.3–10[a]	–	78	11
Moreno Morales et al. (2015) [73]	ps, ob	53	19–73	CSE, NCSE	SE, RSE, SRSE	400	400	57	–
d´Orsi et al. (2015) [74]	ps, sc	23	33–85	CSE, NCSE	SE, RSE, SRSE	200	200–400	80	20
Lang et al. (2016) [75]	ps, mc	51	1–92	CSE, NCSE	SE, RSE, SRSE	300	93–1200	70	13
Santamarina et al. (2018) [76]	rs, mc	165	av. 64	NCSE	SE, RSE	100–600	200–400	63	10
Reif et al. (2018) [77]	rs, sc	1	28	ASE	RSE	400	400	100	0
Ngampoopun et al. (2018) [78]	ps, sc	11	7–16	NCSE	SE, RSE	227	225	73	9
Perrenoud et al. (2017) [79]	rs, mc	40	34–88	–	SE, RSE	100–800	–	40	–

Table 1 (continued)

	Study design			Status epilepticus		Therapy regimen		Outcome	
	Layout	Study population		Type	Severity	Loading dose (mg)	Maintenance dose (mg/day)	Response (%)	AEs (%)
		n	Age (years)						
Newey et al. (2017) [80]	rs, sc	51	av. 60	CSE, NCSE	RSE	188[b]	362[b]	82	–
Toledo et al. (2018) [81]	rs, mc	15	19–81	CSE, NCSE	SE, RSE	100–600	100–800	73	53
(b) Brivaracetam (BRV)									
Strzelczyk et al. (2017) [49]	rs, mc	11	34–85	NCSE, CSE	RSE, SRSE	50–400	100–400	27	0
Kalss et al. (2018) [51]	rs, sc	7	29–79	NCSE, CSE	RSE	50–200	100–300	43	0
Strzelczyk et al. (2018) [52]	rs, mc	2	23–38	ASE	SE	200–300	–	0	–
Aicua-Rapun et al. (2019) [53]	rs, sc	14	33–80	NCSE, CSE	RSE, SRSE	100–200	200–300	50	–
Santamarina et al. (2019) [50]	rs, mc	43	56±32	CSE, NCSE	SE, RSE, SRSE	50–400	–	54	14
(c) Perampanel (PER)									
Redecker et al. (2015) [88]	rs, cs	9	57–82	NCSE	RSE	2–6	–	22	–
Rohracher et al. (2015) [89]	rs, cs	12	60–91	CSE, NCSE	RSE	2–12	4–12	16	0
Beretta et al. (2018) [90]	ps, cs	8	26–71	NCSE	SRSE	6–12	6–12	100	0
Rohracher et al. (2018) [91]	rs, cs	30	18–91	NCSE, CSE	RSE	2–32	12–20	17	0
Newey et al. (2019) [92]	ps, cr	4	28–69	NCSE, GSE	RSE	32	6–12	100	0
Ho et al. (2019) [93]	rs, cs	22	26–89	NCSE, CSE	RSE, SRSE	2–8	2–12	36	–
Rhabani et al. (2019) [94]	rs, cr	1	72	CSE	SRSE	8	–	100	–
Santamarina et al. (2019) [95]	ps, cr	3	19–39	CSE, NCSE	RSE	8–16	–	100	0
Strzelczyk et al. (2019) [87]	rs, mc	52	19–91	NCSE, CSE	RSE, SRSE	2–24	4–24	37	4
(d) Stiripentol (STP)									
Strzelczyk et al. (2015) [96]	rs, sc	5	65–88	CSE, NCSE	SRSE	2000–5000	4000–6000	60	0
Uchida et al. (2017) [98]	rs, sc	1	20	NCSE	RSE	500	2500	–	0
Uchida et al. (2018) [99]	rs, sc	5	18–65	–	SRSE	500	2500	100	0
(e) Lamotrigine (LTG)									
Pisani et al. (1991) [83]	rs, sc	1	17	CSE	RSE	600	400	100	0
(f) Topiramate (TPM)									
Kahriman et al. (2003) [100]	rs, sc	3	0–11	CSE, NCSE	RSE	2–3[a]	5–6[a]	100	0
Bensalem and Fakhoury (2003) [101]	rs, sc	3	31–75	CSE	RSE, SRSE	500	200–500	67	–
Blumkin et al. (2005) [102]	rs, sc	2	0	CSE	RSE	2–5[a]	22–25[a]	100	0

Table 1 (continued)

	Study design			Status epilepticus		Therapy regimen		Outcome	
	Layout	Study population		Type	Severity	Loading dose (mg)	Maintenance dose (mg/day)	Response (%)	AEs (%)
		n	Age (years)						
Perry et al. (2006) [103]	ps, sc	3	0–6	CSE	RSE	10[a]	5[a]	100	–
Soler et al. (2009) [104]	rs, sc	3	24–59	–	RSE	–	–	100	–
Akyildiz and Kumandas (2011) [105]	ps, sc	14	1–12	CSE	RSE, SRSE	5[a]	5[a]	86	21
Kim et al. (2011) [106]	rs, sc	16	31–79	CSE, NCSE	SE, RSE	300–1000	–	81	0
Synowiec et al. (2011) [107]	rs, sc	35	19–84	–	RSE, SRSE	100–1000	100–800	40	0
Bragatti et al. (2011) [108]	rs, sc	1	16	CSE	RSE	2,5[a]	2,5[a]	100	–
Hottinger et al. (2012) [109]	rs, sc	35	19–83	CSE, NCSE	RSE, SRSE	800[c]	800[c]	71	–
Stojanova and Rossetti (2012) [110]	rs, sc	11	16–80	CSE	RSE, SRSE	–	50–800	18	–
Shelton et al. (2014) [111]	rs, sc	1	12	CSE	RSE	–	1000	100	0
Asadi-Pooya et al. (2015) [112]	ps, sc	20	18–92	CSE	RSE, SRSE	–	–	25	–
Madzar et al. (2016) [113]	rs, sc	17	37–70	CSE, NCSE	RSE, SRSE	50–400	150–1000	100	–
Fechner et al. (2019) [114]	rs, mc	106	18–95	CSE, NCSE	RSE, SRSE	25–500	25–900	27	36
(g) Oxcarbazepine (OXC)									
Kellinghaus et al. (2014) [85]	rs, sc	13	56–86	CSE	RSE	600–1800	1200–2400	62	23
(h) Zonisamide (ZNS)									
Hubert et al. (2020) [116]	rs, mc	34	19–91	CSE, NCSE	SE, RSE, SRSE	25–300	25–600	16	10

AEs adverse events, *ASDs* antiseizure drugs, *ASE* absence SE, *av* average, *cs* case series, *CSE* convulsive SE, *cr* case report, *mc* multicenter, *NCSE* nonconvulsive SE, *ob* observational, *ps* prospective, *rs* retrospective, *RSE* refractory SE, *sc* single-center, *SE* status epilepticus, *SRSE* super-refractory SE

[a]Milligrams/kilogram body weight

[b]Average dose

[c]Up to

AEs have been reported in 0–77% of the enrolled patients, with bradycardia, hypotension, and relevant atrioventricular blockage as relevant substance-specific symptoms [55–81]. The largest retrospective multicenter cohort enrolled 165 patients with SE/RSE and reported a responder rate of 63% as well as good tolerability, with 10% of subjects reporting AEs [76]. Given this review focuses on patients in a PCS or with a LOT, one publication with a cohort of 15 adult patients with active cancer of various etiologies and SE/RSE has to be highlighted. Here, a responder rate of 54% and AEs in 14% of the enrolled subjects were reported [81].

According to the current state of knowledge, a loading dose of 5 mg/kg (200–400 mg) or greater and a maintenance dose of 200–400 mg/day seem feasible (Table 1a).

LTG is a third-generation ASD approved for use in FE and genetic generalized epilepsy (GGE) as well as in Lennox–Gastaut syndrome, albeit available in oral tablet form only. Via the modulation of Na^+ channels, LTG suppresses the release of glutamate and aspartate as the dominant excitatory neurotransmitters. Based on its strong potential for interactions as well as the high risk of life-threatening skin reactions, including Stevens–Johnson syndrome,

drug reaction with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, LTG must be titrated slowly, usually requiring weeks to reach a therapeutic dosage [82]. Moreover, LTG has a high interaction potential with other drugs due to its exceptional hepatic metabolization. There is only one reported case of the successful use of LTG in RSE, from 1991 [83]. However, due to the mentioned aspects, there is currently no evidence supporting the efficacy, safety, or tolerability of LTG (Table 1e).

OXC is a third-generation ASD derivate of CBZ and a member of the dibenzazepine family approved for FE. OXC is a prodrug that is metabolized to its pharmacologically active derivate licarbazepine (MHD), which acts mainly by inactivating voltage-gated Na^+ channels. OXC is available as both a tablet and oral solution. Moreover, an anticonvulsive effect via enhanced potassium conductance and the modulation of voltage-gated calcium channels has been reported for this medication [84]. OXC is currently not approved for SE and there is only one retrospective case series with 13 enrolled adult patients supporting its efficacy, safety, and tolerability in RSE, with a responder rate of 62%. AEs, especially hyponatremia, were reported in 23% of patients [85]. According to the current state of knowledge, a loading dose of 600 mg and a maintenance dose of between 600 and 1800 mg/day seem feasible (Table 1g).

PER is one of the newest established third-generation ASDs. It is approved as add-on therapy in FE and GGE, and is available as both a tablet and oral formulation (with an intravenous solution under development). PER acts as a noncompetitive antagonist at AMPA receptors [37]. Regarding the considerable glutamatergic proportion in the pathomechanism of SE [86], PER was granted special interest in the context of RSE and SRSE [37, 86, 87]. PER is not approved for use in SE but nine published case series and reports involving a total of 141 patients with CSE and NCSE are available that suggest a responder rate of 16–100% [87–95]. The largest available retrospective, multicenter study with 53 adult patients reports a responder rate of 37% and good tolerability, with only sporadic AEs in 8% (4/53) of the enrolled subjects [87]. According to the current state of knowledge, a loading dose of between 8 and 12 mg (up to 32 mg in few reported cases) and a maintenance dose of 10–12 mg/day seem feasible (Table 1c).

STP is currently only approved for administration in patients with Dravet syndrome and refractory generalized tonic–clonic seizures as add-on therapy with VPA and clobazam, and is available only for oral application as a tablet or dissoluble granulate. STP acts mainly via activating the subunits α3 and δ of $GABA_A$ receptors. In addition, STP has been shown to increase extracellular GABA concentration via an unknown mechanism [96]. Being metabolized via the hepatic cytochrome P450 isoenzymes, STP secondarily increases the serum concentrations of many other ASDs, such as CBZ, VPA, PHT, and PB and many BZDs, supporting additional anticonvulsive properties [97]. There are three case reports or series in RSE/SRSE involving a total of 11 adult patients, revealing a responder rate of 0–100% as well as good tolerability of the treatment [96, 98, 99]. The largest case series includes five elderly patients between 65 and 88 years of age, and reports a responder rate of 60% without any AEs [96]. According to the current state of knowledge, a loading dose of 2000–4000 mg and a maintenance dose of 2000–3000 mg/day seem feasible. However, the comparably expensive costs of STP of approximately €100 ($110 or £85) per day have to be considered (Table 1d).

TPM is an orally available third-generation ASD approved for monotherapy and add-on therapy in FE and GGE that acts mainly via the modulation of voltage-gated Na^+ channels, and also via calcium channels, by increasing GABA levels and antagonism at the excitatory AMPA receptors. In both FE and GGE, TPM has been proven to be an effective and well-tolerated therapeutic option. TPM is not approved for use in SE. To date, there are 15 case reports and series with a total of 268 pediatric and adult subjects with RSE/SRSE and a responder rate of 17–100% [100–114]. AEs (predominantly hyperammonemia) in seven reports (47%), with a frequency of between 0 and 36%, were reported, mostly during the simultaneous intake of VPA [100, 102, 105–107, 111, 114]. The largest retrospective multicenter study enrolled 106 adult patients and reported a responder rate of 27%, as well as AEs in 36% of patients, additionally confirming the risk for relevant hyperammonemia in patients being simultaneously treated with VPA or PB [114]. Moreover, metabolic acidosis has been reported as a frequent AE [115]. According to the current state of knowledge, a loading dose of 100–200 mg and a maintenance dose of 200–600 mg/day, or 2–5 mg/kg and 5 mg/kg in pediatric patients, seem feasible (Table 1f).

ZNS is a third-generation ASD approved as add-on therapy in FE with seizures with or without secondary generalization. ZNS is only available as an oral formulation and unfolds its anticonvulsive effect most likely via the modulation of voltage-gated Na^+ and T-type calcium channels. To date, only one study is available comprising 34 patients with SE using a median ZNS maintenance dose of 400 mg/day after loading with a median dose of 100 mg. A clinical effect attributed to ZNS was observed in 16.2% of the SE patients, and possible AEs occurred in 10.4% of the cohort [116].

3.3 Other Minimally or Non-Invasive Therapeutic Options

$MgSO_4$ is a well-established prophylactic and therapeutic option in pregnant patients with pre-eclampsia and eclampsia-associated seizures; however, its use in non-eclamptic RSE is not approved [26]. Although its exact anticonvulsive

mechanism of action is not well-understood at this time, MgSO$_4$ is supposed to modulate and thereby inhibit N-methyl D-aspartate (NMDA) receptors. Regarding its use in non-eclamptic RSE/SRSE, 23 case reports and case series involving a total of 32 adult and pediatric patients are available. A response to MgSO$_4$ was reported in 38% (12/32) of patients, while 47% (7/15) showed a recurrence of seizures after discontinuation. AEs were addressed in four reports, including in detail in three of four subjects (75%) [117–139]. In general, the use of MgSO$_4$ has been controversially discussed by modern epileptologists; a bolus of 4 g followed by a continuous infusion of 2–6 g/h is thought to increase the serum Mg level by approximately 3.5 mmol/L and has been suggested as appropriate (Table 2) [1, 2, 26].

The KD is a subtype of low-carb, high-fat and high-protein nutrition used as an established therapeutic approach in GLUT-1 deficiency and pyruvate dehydrogenase deficit, as well as refractory epilepsy. KD unfolds its anticonvulsive action by way of offering a limited neuronal energy supply, thereby prompting a general decrease in neuronal excitability. The presence of ketones in the blood and urine can be used as an indicator of a sufficient nutrition change. In the area of RSE and SRSE, 30 publications including a total of 157 pediatric and adult patients are available, using mainly KD in a 3:1 to 5:1 ratio (27/30; 90%) [27, 31, 98, 132, 140–165]. KD is usually initiated as an enteral solution but may also be induced by intravenous means [132]. Moreover, the sparse use of low glycemic index treatment, the adoption of medium-chain triglycerides, and additional use of an SGLT-2 inhibitor in a case of insufficient ketosis under KD have been reported (each 1/30; 3%) [145, 160, 164]. Overall, 80% (125/157) of patients were responders and relevant AEs were observed in 47% (55/117), including mostly gastroesophageal reflux, acidosis, or lipid/electrolyte unbalance. However, AEs were not addressed in all included publications (Table 3).

Neurosteroids with allopregnanolone (brexanolone) as the main representative of this class are endogenous derivates of progesterone acting mainly as positive allosteric modulators at the GABA$_A$ receptors. Allopregnanolone has

Table 2 Overview of the current evidence for the use of magnesium sulfate (MgSO$_4$) in refractory and super-refractory status epilepticus

	Study design			Status epilepticus		Therapy regimen		Outcome	
	Layout	Study population		Type	Severity	Duration of treatment (days)	Recurrence after withdrawal	Response (n/n)	AEs (n/n)
		n	Age (years)						
Baxter et al. (2003) [117]	rs, sc	1	6	CSE	RSE	–	–	0/1	–
Berkley et al. (2015) [118]	rs, sc	1	23	CSE	RSE	–	–	0/1	–
Broomall et al. (2014) [119]	rs, sc	1	11	CSE	RSE	4	–	0/1	–
Dionisio et al. (2013) [120]	rs, sc	1	17	CSE	RSE	–	–	0/1	–
Fisher et al. (1988) [121]	rs, sc	1	22	CSE	RSE	2	1/1	0/1	1/1
Gedik et al. (2014) [122]	rs, sc	1	5	CSE	RSE	4	–	0/1	–
Nandakumar et al. (2008) [123]	rs, sc	1	24	CSE	RSE	–	–	0/1	–
Neligan et al. (2011) [124]	rs, sc	1	33	–	SE, RSE	–	0/1	1/1	–
Pandey et al. (2010) [125]	rs, sc	1	18	CSE	RSE	5	–	0/1	–
Robakis and Hirsch (2006) [126]	rs, sc	1	30	CSE	RSE	7	–	0/1	–
Sadeh et al. (1991) [127]	rs, sc	1	16	CSE	RSE	7	1/1	1/1	1/1
Sahin et al. (2001) [128]	rs, sc	2	13, 15	CSE	RSE	–	–	1/2	–
Savard et al. (2012) [129]	rs, sc	1	27	CSE	RSE	–	–	0/1	–
Shin et al. (2011) [130]	rs, sc	1	57	NCSE	RSE	1	0/1	1/1	–
Storchheim (1933) [131]	rs, sc	8	–	–	SE, RSE	–	4/8	4/8	–
Strzelczyk et al. (2013) [132]	rs, sc	1	21	CSE	RSE	1	–	0/1	1/1
Tan et al. (2013) [133]	rs, sc	1	2	CSE	RSE	–	0/1	1/1	0/1
Valle-Morales et al. (2009) [134]	rs, sc	1	29	CSE	RSE	–	–	0/1	–
Visser et al. (2011) [135]	rs, sc	2	19,17	CSE	RSE	6	1/2	2/2	–
Madisia and Bergkeley (2014) [136]	rs, sc	1	23	CSE	RSE	–	–	0/1	–
Zaatreh (2005) [137]	rs, sc	1	48	CSE	RSE	–	–	1/1	–
Hatch et al. (2016) [138]	rs, sc	1	31	CSE	RSE	–	–	1/1	–
Sahin and Riviello (2001) [139]	rs, sc	1	15	CSE	RSE	–	–	0/1	–

AEs adverse events, *CSE* convulsive SE, *NCSE* nonconvulsive SE, *rs* retrospective, *RSE* refractory SE, *sc* single-center study, *SE* status epilepticus

Table 3 Overview of the current evidence for the use of a ketogenic diet in refractory and super-refractory status epilepticus

	Study design		Status epilepticus		Therapy regimen		Outcome	
	Layout	Study population	Type	Severity	Diet type	Achieved level of ketosis (n/n)	Response (n/n)	AEs (n/n)
		n	Age (years)						
Bodenant et al. (2008) [140]	rs, sc	1	54	CSE	RSE	KD 4:1	1/1		–
Wusthoff et al. (2010) [141]	rs, sc	2	29–34	CSE, NCSE	SRSE	KD 4:1	2/2	2/2	–
Nabbout et al. (2010) [142]	rs, sc	9	0–6	CSE	RSE	KD 4:1	8/9	7/9	–
Cervenka (2011) [31]	rs, sc	1	49	FSE	SRSE	KD 4:1	1/1	1/1	–
Kramer et al. (2011) [143]	rs, mc	4	7–27	–	SRSE	–	–	1/4	–
Nam et al. (2011) [144]	ps, sc	5	4–40	–	RSE	KD 4:1	5/5	5/5	5/5
Martikainen et al. (2012) [145]	rs, sc	1	22	CSE	SRSE	LGIT	–	1/1	0/1
Vaccarezza et al. (2012) [146]	rs, sc	5	1–14	CSE	SRSE	–	–	4/5	–
Sort et al. (2013) [147]	rs, sc	3	3–11	CSE	SRSE	–	3/3	2/3	1/3
Strzelczyk et al. (2013) [132]	rs, sc	1	26	CSE	SRSE	KD 4:1	1/1	1/1	–
Caraballo et al. (2014) [148]	rs, sc	10	0–16	CSE	SRSE	KD 4:1	10/10	7/10	3/10
Cobo et al. (2014) [149]	rs, sc	4	0–13	CSE	SRSE	KD 4:1	4/4	4/4	1/4
Thakur et al. (2014) [150]	rs, mc	10	23–51	–	SRSE	KD 3–4:1	9/10	9/10	3/10
Amer et al. (2015) [151]	rs, sc	1	21	–	SRSE	KD 4:1	1/1	1/1	–
Caraballo et al. (2015) [152]	rs, sc	2	0–1	CSE	SRSE	KD 4:1	2/2	2/2	0/2
Cash (2015) [153]	rs, sc	1		CSE	SRSE	KD 4:1	1/1	1/1	–
Fung et al. (2015) [154]	rs, sc	4	8–16	CSE	SRSE	KD 4:1	3/4	1/4	2/4
Lin et al. (2015) [155]	rs, sc	1	6	CSE	SRSE	KD 4:1	1/1	1/1	
Appavu et al. (2016) [27]	rs, sc	10	2–16	CSE	SRSE	KD 4–5:1	9/10	9/10	1/10
Caraballo et al. (2017) [156]	rs, sc	6	2–9	CSE	RSE	KD 4:1	–	5/6	0/6
Cervenka et al. (2017) [157]	ps, mc	15	18–82	–	SRSE	KD 4:1	15/15	11/15	10/15
Smith and Press (2017) [158]	rs, sc	9			SRSE	–	9/9	8/9	2/9
Uchida et al. (2017) [98]	rs, sc	1	20	NCSE	RSE	–	–	1/1	–
Arya et al. (2018) [159]	ps, mc	14	0–19	–	RSE	KD 4:1	14/14	10/14	3/14
Blunk et al. (2018) [160]	rs, sc	1	42	CSE	RSE	KD/SGLT2	1/1	0/1	0/0
Francis et al. (2019) [161]	rs, sc	11	21–73	–	RSE	–	10/11	8/11	10/11
Park et al. (2019) [162]	rs, sc	16	0–21	CSE	RSE	3–4:1	14/16	15/16	10/16
Peng et al. (2019) [163]	rs, sc	7	1–13	–	RSE	3–4:1	6/7	7/7	3/7
Prasoppokakorn et al. (2019) [164]	rs, sc	1	19	CSE	SRSE	MCT KD	1/1	1/1	0/1
Noviawaty et al. (2020) [165]	rs, sc	1	38	CSE	SRSE	KD 4:1	1/1	1/1	

AEs adverse events, *CSE* convulsive SE, *FSE* febrile SE, *KD* ketogenic diet, *LGIT* low glycemic index treatment diet, *mc* multicenter, *MCT KD* medium-chain triglyceride ketogenic diet, *NCSE* nonconvulsive SE, *ps* prospective, *rs* retrospective, *RSE* refractory SE, *sc* single-center, *SE* status epilepticus, *SGLT2* sodium-glucose co-transporter-2, *SRSE* super-refractory SE

faced high expectations as a new potential option to wean patients from anesthetic drugs during the treatment of RSE and SRSE. Three studies with a total of 29 patients have been published to date, showing promising results [119, 166, 167]; however, a placebo-controlled RCT with 132 enrolled subjects (67 receiving verum vs. 65 receiving placebo) analyzing the safety and efficacy of allopregnanolone to wean from third-line ASDs in SRSE was aborted by the sponsor after preliminary results suggested no significant difference was present between the groups ($p = 0.878$). Within the RCT population, allopregnanolone was well-tolerated [168]. Moreover, the use of neurosteroids outside weaning

of intravenous or inhalable anesthetic drugs has not been analyzed thus far.

3.3.1 Other Immunomodulatory or Immunosuppressive Treatment Options (IT)

Over the past decades, several ITs have been used in SE, such as SP, IVIGs or plasmapheresis/plasma exchange (PLEX). Based on their direct effects, these options have been classified as first-line ITs to allow a better differentiation from rituximab, cyclophosphamide, or other long-term immunosuppressants (second-line ITs). There were 72

Table 4 Overview of the current evidence for the use of neurosteroids and immunomodulatory/immunosuppressive treatment in refractory and super-refractory status epilepticus

	Study design			Status epilepticus		Therapy characteristics			Outcome
	Layout (phase)	Study population		Type	Severity	Duration (days)	Loading dose (µg/kg/h)	Rate (µg/kg/h)	Response (n/n)
		n	Age (years)						
(a) Neurosteroids (allopregnanolone)									
Broomall et al. (2014) [119]	rs, sc	2	2, 11	CSE, NCSE	SRSE	5	–	28–86	Successful weaning
Vaitkevicius et al. (2017) [167]	rs, sc	2	23, 28	CSE, NCSE	SRSE	5	–	86	Successful weaning
Rosenthal et al. (2017) [166]	ps, mc (I/II)	25	10–76	–	SRSE	5	286	86–156	17/25
NCT02477618 (2019) [168]	ps, mc (III)	67	41.3	CSE, NCSE	SRSE	6	300	90–150	Not superior to placebo (p = 0.878)
(b) Immunomodulatory/immunosuppressive treatment with SP, IVIG or PLEX									
Agan et al. (2015) [199]	rs, sc	1	19	AI CSE	RSE	PLEX			1/1
Agirre-Arri-zubieta and Moran (2012) [200]	rs, sc	1	28	–	RSE	PLEX, IVMP			0/1
Al-Ajlan et al. (2014) [201]	rs, sc	1	18	AI CSE	RSE	SP, IVIG			0/1
Alam et al. (2013) [202]	rs, sc	1	60	AI CSE	RSE	SP, IVIG, PLEX, RTX			0/1
Alam et al. (2014) [203]	rs, sc	1	20	CSE	RSE	SP, IVIG			0/1
Amer et al. (2015) [151]	rs, sc	1	21	AI CSE	RSE	SP, IVIG, PLEX			0/1
Armas et al. (2013) [204]	rs, sc	1	69		RSE	SP, IVIG, AZA			1/1
Barnes et al. (2013) [205]	rs, sc	1	33	CSE	RSE	SP, PLEX			0/1
Bobb et al. (2014) [206]	rs, sc	1	28	–	RSE	IVIG			1/1
Brigo et al. (2018) [207]	rs, sc	1	22	AI CSE	RSE	SP			1/1
Buenache et al. (2012) [208]	rs, sc	1	4	FIRES	RSE	SP, IVIG, PLEX			1/1
Buerger et al. (2015) [209]	rs, sc	1	74	CSE	RSE	SP, PLEX			0/1
Calabrace and Witherspoon (2014) [210]	rs, sc	1	19	AI NCSE	RSE	SP, PLEX, RTX			0/1
Caputo et al. (2017) [211]	rs, sc	1	13	FIRES	RSE	SP, IVIG			1/1
Caraballo et al. (2013) [212]	rs, sc	10	-	FIRES	RSE	IVIG, PLEX, RTX			3/10
Charles et al. (2014) [213]	rs, sc	1	57	NCSE	RSE	IVIG			1/1
Chevret et al. (2008) [214]	rs, sc	4	9[a]	FIRES	RSE	PLEX			1/4
Chevret et al. (2011) [215]	rs, sc	8	6[a]	FIRES	RSE	PLEX			1/8

Table 4 (continued)

	Study design			Status epilepticus		Therapy characteristics			Outcome
	Layout (phase)	Study population		Type	Severity	Duration (days)	Loading dose (µg/kg/h)	Rate (µg/kg/h)	Response (n/n)
		n	Age (years)						
Costas et al. (2015) [216]	rs, sc	1	5	FIRES	RSE	IVIG, PLEX			0/1
Dishong et al. (2013) [217]	rs, sc	1	14	FIRES	RSE	SP, IVIG, PLEX, Anakinra			0/1
Gall et al. (2013) [218]	rs, sc	2	30[a]	NORSE	RSE	PLEX, IVIG			2/2
Gedik et al. (2014) [122]	rs, sc	1	5	AI CSE	RSE	SP, PLEX			1/1
Ghamande et al. (2013) [219]	rs, sc	1	41	–	RSE	SP, IVIG, RTX			0/1
Gonzales et al. (2011) [220]	rs, sc	1	23	NORSE	RSE	SP, IVIG			0/1
Hainsworth et al. (2014) [221]	rs, sc	1	23	AI CSE	RSE	IVIG, SP, PLEX, RTX			1/1
Hakimi et al. (2014) [222]	rs, sc	1	44	AI CSE	RSE	SP, IVIG, PLEX			1/1
Hoang et al. (2014) [223]	rs, sc	1	40	NCSE	RSE	IVIG, SP, PLEX			0/1
Howell et al. (2012) [224]	rs, sc	1	14	FIRES	RSE	PLEX, RTX			0/1
Hribljan et al. (2013) [225]	rs, sc	4	–	FIRES	RSE	SP, IVIG, PLEX			0/4
Incecik et al. (2015) [226]	rs, sc	1	16	–	RSE	SP, IVIG, PLEX			0/1
Kaneko et al. (2012) [227]	rs, sc	1	17	AI CSE	RSE	SP, IVIG, PLEX			1/1
Katsuse et al. (2019) [228]	rs, sc	1	48	AI NCSE	RSE	SP			1/1
Khawaja et al. (2014) [229]	rs, sc	1	22	AI CSE	RSE	IVIG, SP, PLEX, RTX			1/1
Khawaja et al. (2015) [230]	rs, sc	7	35[a]	AI/viral CSE	RSE	IVIG, SP, PLEX, RTX			0/7
Kirkpatrick et al. (2011) [231]	rs, sc	1	19	AI CSE	RSE	SP, PLEX, RTX			1/1
Kong et al. (2018) [232]	rs, sc	24	17[a]	AI CSE	RSE	SP, IVIG, PLEX, RTX, CP			20/24
Korff et al. (2009) [233]	rs, sc	1	9	FIRES	RSE	SP, PLEX			0/1
Kramer et al. (2011) [234]	rs, sc	1	–	FIRES	RSE	SP, IVIG, PLEX			0/1
Labate et al. (2013) [235]	rs, sc	1	17	AI CSE	RSE	SP, IVIG			1/1
Le Moigno et al. (2014) [236]	rs, sc	1	6	AI CSE	RSE	SP, PLEX, RTX			1/1
Lenoir et al. (2012) [237]	rs, sc	1	17	AI CSE	RSE	SP, IVIG, PLEX			1/1
Li et al. (2013) [238]	rs, sc	3	39, 43, 51	CSE, NCSE	RSE	SP, IVIG			2/3

Table 4 (continued)

	Study design			Status epilepticus		Therapy characteristics			Outcome
	Layout (phase)	Study population		Type	Severity	Duration (days)	Loading dose (µg/kg/h)	Rate (µg/kg/h)	Response (n/n)
		n	Age (years)						
Lin et al. (2018) [239]	rs, sc	45	1–18	CSE	RSE	SP, IVIG vs. IVIG			10/45
Lousa et al. (2000) [240]	rs, sc	1	14	–	RSE	PLEX			1/1
Madisi and Berkley (2014) [241]	rs, sc	1	23	NORSE, CSE	RSE	IVIG, SP, PLEX, RTX			1/1
Malaga et al. (2015) [242]	rs, sc	1	1	AI CSE	RSE	SP, IVIG, PLEX, RTX			1/1
Mann et al. (2013) [243]	rs, sc	1	20	AI CSE	RSE	IVIG, SP, PLEX			1/1
Marques et al. (2014) [244]	rs, sc	1	30	AI CSE	RSE	SP, IVIG			1/1
Milh et al. (2012) [245]	rs, sc	1	5	AI CSE	RSE	IVIG			1/1
Mirás Veiga et al. (2016) [246]	rs, sc	1	4	FIRES	RSE	SP, PLEX, IVIG			0/1
Moeller et al. (2012) [247]	rs, sc	1	27	AI CSE	RSE	IVIG, PLEX			0/1
Nakamura (2015) [248]	rs, sc	1	1	FIRES	RSE	SP, IVIG, PLEX			0/1
Neligan et al. (2011) [124]	rs, sc	1	33	AI CSE	RSE	IVIG, RTX			1/1
Noviawaty et al. (2015) [249]	rs, sc	1	13	AI CSE	RSE	PLEX			0/1
Ogawa et al. (2013) [250]	rs, sc	1	11	AERRPS	RSE	PLEX			0/1
Pari et al. (2014) [251]	rs, sc	1	19	AI NCSE	RSE	SP, PLEX			1/1
Ramos et al. (2019) [169]	rs, sc	4	51–75	CSE, NCSE	RSE	SP			4/4
Rypulak et al. (2016) [252]	rs, sc	1	23	AI CSE	RSE	IVIG, SP,			1/1
Sawicka et al. (2016) [253]	rs, sc	1	18	AI CSE	RSE	IVIG, PLEX, RTX			1/1
Shatzmiller et al. (2011) [254]	rs, sc	1	19	AI CSE	RSE	SP, IVIG, PLEX			1/1
Shrivastava et al. (2017) [255]	rs, sc	1	24	NORSE	RSE	SP, IVIG, PLEX			1/1
Soldatos and Gorman (2012) [256]	rs, sc	1	6	FIRES	RSE	SP, IVIG, PLEX			1/1
Thomas et al. (2012) [257]	rs, sc	1	19	AI NCSE	RSE	SP, IVIG, PLEX			1/1
Ting et al. (2017) [258]	rs, sc	1	16	AI CSE	RSE	SP, PLEX, CP			1/1
Triplet et al. (2018) [259]	rs, sc	1	21	AI CSE	RSE	SP, IVIG, PLEX, RTX, CP			1/1

Table 4 (continued)

	Study design			Status epilepticus		Therapy characteristics			Outcome
	Layout (phase)	Study population		Type	Severity	Duration (days)	Loading dose (μg/kg/h)	Rate (μg/kg/h)	Response (n/n)
		n	Age (years)						
Van Baalen et al. (2012) [260]	rs, sc	6	2–12	FIRES	RSE	SP, IVIG, PLEX			1/6
Villani et al. (2001) [261]	rs, sc	1	45	CSE	RSE	SP, IVIG, PLEX			1/1
Wilder-Smith et al. (2005) [262]	rs, sc	3	–	NORSE, CSE	RSE	IVIG			0/1
Yamamoto et al. (2014) [263]	rs, sc	1	35	AI CSE	RSE	SP, IVIG, PLEX			1/1
Yeo et al. (2009) [264]	rs, sc	1	32	AI CSE	RSE	IVIG			1/1
Yoshida et al. (2019) [265]	rs, sc	1	68	PNS NCSI	RSE	SP, PLEX			1/1

AERRPS acute encephalitis with refractory repetitive partial seizures, *AI* autoimmune, *AZA* azathioprine, *CP* cyclophosphamide, *CSE* convulsive SE, *FIRES* febrile infection-related epilepsy syndrome, *IVIG* intravenous immunoglobulins, *mc* multicenter study, *NCSE* non-convulsive SE, *NORSE* new-onset refractory status epilepticus, *PLEX* plasma exchange or plasmapheresis, *PNS* paraneoplastic neurological syndrome, *ps* prospective, *rs* retrospective, *RSE* refractory SE, *RTX* rituximab, *sc* single-center, *SE* status epilepticus, *SP* steroid pulse, *SRSE* super-refractory SE

[a]Median

studies with 175 patients who used first-line ITs, of which 14 (19%) used a single therapy regimen, 20 (28%) used a double therapy regimen, and 38 (53%) used a triple or quadruple therapy regimen. Overall, 46% (n = 81) of the patients treated with IT showed an attributable response. The data situation was insufficient to allow for analyzing the AEs. For more information on the included studies, please refer to Table 4.

4 Discussion

Based on a survey of existing publications, no level 1, grade A evidence is available for the use of any of the reviewed fourth-line ASDs in RSE. The best data were found for LCM and TPM, with a level 3 evidence and grade C recommendation. Moreover, there was level 4, grade D evidence for the use of BRV and PER, or level 5, grade D evidence for STP, OXC, and ZNS in RSE. Regarding the other assessed minimally or non-invasive, non-medicinal therapeutic options, level 4, grade D evidence supporting the benefit of the KD, and level 5, grade D evidence supporting the use of MgSO$_4$, in the context of non-eclamptic RSE, were available. The evidence for ITs, such as SP, IVIG, or PLEX, was level 4, grade D, with the additional limitation that most studies showing an effect of ITs included patients with autoimmune

SE. Even if single studies supported the hypothesis, the SP use could be a feasible option as an abortive treatment for refractory seizures or status epilepticus [169], but is no reliable evidence for their broad use in RSE in general [170]. There were contradictory results and no reliable evidence regarding the use of neurosteroids in RSE, with the evidence formally rated as level 5, grade D (Table 4). Based on these results, the use of neurosteroids in RSE treatment cannot be recommended (Table 4), although studies of ganaxolone in humans are in progress [171]. All mentioned medicinal or non-medicinal therapeutic options do not require a stay in the ICU or other invasive measures beyond demand-oriented continuous monitoring that is usually affected by ACP or LOT, or within a moderate PCS. Regarding PLEX, establishing a central venous catheter, as well as the often-exhausting experience of therapeutic cycles, has to be reflected upon and discussed in regard to the individual advance directives. Nearly all reviewed therapy options can be applied orally or enterally via a nasogastric tube, which underlines their applicability in patients with impairment of consciousness as well as dysphagia or aphagia. Due to rarely reported cardiac arrhythmia or de novo atrioventricular blockage [26], MgSO$_4$ should be applied intravenously for improved controllability and to prepare for the possibility of rapid discontinuation in the case of the above-mentioned symptoms. Due to the obligatory need for advanced cardiopulmonary

monitoring of established anesthetic drugs, such as keta-mine, propofol, thiopental or midazolam, in low doses and not requiring mechanical ventilation, they were not included in this systematic review but may also be individually considered [2, 172, 173]. For the same reasons, sporadically used neuromodulation techniques in RSE, such as vagal nerve stimulation (VNS), electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS) were also not included in this review [174, 175].

As with any systemic review, this publication may suffer from several methodical limitations, such as possible missing relevant publications not identified by the prescribed search algorithm or the cross-check via pre-existing reviews on this topic. Moreover, the exclusion of articles not available in the English, French, German, Italian, or Spanish languages, as well as the limitation of the research on the MEDLINE, EMBASE and Cochrane databases, represents possible biases of this review. In particular, all studies on RSE and SRSE are subject to bias due to consecutive add-on therapy with several ASDs or other therapeutic options, which makes it difficult to link a specific effect to one of the used interventions. Most included publications try to solve this bias by temporal correlation of therapy onset and the observed effect; however, this established way of analysis does not exclude the occurrence of a prolonged effect of previously used interventions or a cumulative effect of different therapeutic approaches [176, 177]. To minimize the mentioned limitations and to offer a structured analysis, PRISMA guidelines were closely followed [178].

The management of RSE in patients with a LOT or a PCS represents a challenge for modern clinicians, intensive care medics, and epileptologists. Due to patients' advanced directives or specific health conditions, recommendations of existing guidelines have to be frequently omitted as invasive treatment in the ICU may be refused or individual contraindications for specific second- or third-line treatment options exist. In the case of a sustained wish for a conservative therapeutic attempt, clinicians have to fall back on fourth-line ASDs as the last therapeutic resort. The evidence for the use of fourth-line ASDs in RSE and SRSE is limited; however, there are several therapeutic options that have been shown to be effective, safe, and well-tolerated whose use can be translated in the context of ACP, LOT, and PCS. In accordance with frequent ACP, LOT or PCS, all ASDs as well as KD can be applied enterally without the need to adopt invasive measures such as a central venous catheter or port catheter. In all patients, basal therapy with BZDs should be initiated if possible [19, 179]. The highest level of evidence in RSE/SRSE exists to support the use of LCM and TPM (level 3, grade C), which have been proven to be effective and well-tolerated in patients with RSE [36, 114]. Moreover, there is sufficient evidence for the use of PER (level 4, grade D) [87],

BRV (level 4, grade D), OXC (level 5, grade D) [85], ZNS (level 5, grade D) and STP (level 5, grade D) [96] in patients with RSE or SRSE (Table 1). Here, the reduced potential for psychobehavioral adverse effects, as well as the availability of an intravenous formulation for BRV and the pleiotropic effects of STP, have to be mentioned [37, 96]. The use of LTG, ESL, and CBZ cannot be recommended based on the current state of knowledge. In line with conventional clinical experience, data from rodent studies suggested that early and aggressive combination therapy in RSE treatment is beneficial, which was attributed to an early maladaptive internalization of synaptic $GABA_A$ receptors and the externalization of NMDA receptors [180]. Here, the unique mode of action of LEV, BRV, PER or STM could be of particular advantage, which has to be further elucidated by future trials and research work [37, 96]. However, even if these aspects should not be the focus of the therapy decision, economic aspects of different ASD may also have to be considered [181, 182].

Considering non-medicinal therapeutic options, there is low evidence for the use of KD (level 4, grade D) in RSE based on more than 150 reported cases. This therapy should be started and monitored by a physician experienced in KD, or a nutritional expert, to avoid electrolyte or vitamin imbalance or hypoglycemia, and standardized protocols should be followed [157]. A recent study on the nutritional state in SE showed that the induction of ketogenesis might improve treatment outcomes and will surely stimulate the conduct of further research into the adoption of KD in SE [183]. The use and benefits of $MgSO_4$ in non-eclamptic RSE are controversially discussed within the field [26, 184] and are only supported by weak evidence (level 5, grade D). There is currently no evidence available for the use of neurosteroids in RSE, and, furthermore, there is even evidence against their use [168]. The use of immunotherapies such as steroids, plasmapheresis, or IVIGs also cannot be recommended unless an autoimmune or paraneoplastic etiology is proven or seems obvious [185, 186].

Following the GRADE classification, the authors of this manuscript came to a consensus for a 'high' recommendation for the use of LCM, TPM, and BRV; a 'moderate' recommendation for the use of PER and STM; a 'low' recommendation for the use of OXC, ZNS, and KD; and a 'very low' recommendation for the use of $MgSO_4$ and ITs in patients without presumptive autoimmune etiology of SE. The level of evidence, grade of recommendation, feasible loading and maintenance doses, route of application, and relevant AEs for every mentioned therapeutic option are given in Table 5.

In otherwise healthy patients with RSE/SRSE, rational diagnostics tests should be performed to identify the possible causes or factors leading to disease persistence. According to the German clinical practice guidelines on SE, routine

Table 5 Feasible non- or minimally invasive therapeutic options for RSE in patients undergoing LOT or in a PCS, beyond current recommendations of existing guidelines

Substance		Level of evidence		Dosing		Application	Application	Important treatment issues
Name	INN	Oxford [42]	GRADE [43]	Loading (mg)	Maintenance (mg/day)	Regimen	Route	
Antiseizure drugs								
Topiramate[a]	TPM	3C	I	400	400–600	bid	po/os	Hyperammonemia, metabolic acidosis
Brivaracetam[a]	BRV	4D	I	2[b]	100–200	bid	po/os/iv	Psychobehavioral changes
Perampanel[a]	PER	4D	II	8–12	8–12	qd	po/os	Dizziness, vertigo
Lacosamide[a]	LCM	3C	I	5[b]	200–400	bid	po/os/iv	AV block ≥ °III, relevant bradycardia
Stiripentol[a]	STP	5D	II	2000–3000	3000–4000	bid	po/os	High daily treatment costs
Oxcarbazepine[a]	OXC	5D	III	600–1200	1200–1800	bid	po/os	Hyponatremia
Zonisamide[a]	ZNS	5D	III	200–300	200–600	bid	po/os	Ataxia, skin rash
Other minimally or non-invasive therapeutic options								
Magnesium sulfate	MgSo4	5D	IV	4000	2000–6000[c]	cont	iv	Cardiac arrhythmia
Ketogenic diet[a]	KD	4D	III	KD 4:1 ratio	KD 4:1	cont	po	Acidosis, lipid or electrolyte disbalance, GER
Steroid pulse[a]	IVMP	4D	III	1000–2000	1000–2000	qd	iv	Only if autoimmune etiology is assumed or confirmed
Immunoglobulins[a]	IVIG	4D	III	2[d]		tid	iv	Only if autoimmune etiology is assumed or confirmed
Plasma exchange[a]	PLEX	4D	III	NA	NA	daily	iv	Only if autoimmune etiology is assumed or confirmed

AV atrioventricular, *bid* twice daily, *Cont.* continuous application, *GER* gastroesophageal reflux, *GRADE* Grading Recommendations Assessment, Development, and Evaluation, *iv* intravenous, *IVMP* intravenous methylprednisolone, *KD* ketogenic diet, *LOT* limitation of life-sustaining therapy, *NA* not applicable, *os* oral solution available, *po* orally, *PCS* palliative care setting, *qd* once daily, *RSE* refractory status epilepticus, *tid* three times daily

[a]Use and dose recommendations not in line with the official approval

[b]Milligram/kilogram body weight

[c]Grams/hour as a continuous infusion

[d]Grams/kilogram body weight, distributed over 2–5 days

point-of-care and laboratory testing (including blood glucose, hemography, inflammation parameters, electrolytes, liver, pancreas, renal and thyroid function, and creatine kinase) and cerebral imaging (e.g. computed tomography, magnetic resonance imaging) should be performed, supplemented by lumbar puncture where appropriate. Possible causal, maintenance or trigger factors for RSE/SRSE should be addressed and treated adequately as long as the therapy administered is consistent with the patient's ACP, LOT, or PCS [5, 187].

More so than in any other population, ACP, advance directives, and medical ethical aspects have to be considered carefully in these patients before the initiation of therapy, and should be re-evaluated during the course of treatment.

According to the literature, only a small portion (4.6–39.0%) of patients with SE or other critical neurological diseases had written advance directives or directives disclosed by designated healthcare agents (also known as healthcare proxy, i.e. a person who can act and decide on medical matters if you are not able to do so yourself), which were mostly effecting a do-not-resuscitate (DNR) order [188–190]. Here, the availability of an informed healthcare agent was associated with a slightly increased proportion of patients with DNR orders. Advance directives are largely accepted by physicians regarding both the adaption of the therapy setting and the withholding of resuscitation [190].

Realistic expectations of the outcome of treatment and the timely anticipation of a further disease course are warranted.

In this context, the potential harm of prolonged iatrogenic coma and its secondary risks due to supportive aids and medications (e.g. vasopressors, paralysis of the bowels) that have been previously shown in elderly and multimorbid patients has to be addressed [190–193]. Referring to the written advance directive directly or indirectly (through conversation) will guide the therapeutic approach, with treatment steps checked for their compatibility and discussed with the patient, caregivers, or healthcare agents. For example, before introducing artificial enteral feeding via a nasogastric tube or intravenously as an indispensable step for the KD, it should be considered whether the patient would have agreed to this procedure and artificial nutrition itself, and whether the resulting decrease in quality of life due to both measures would have been accepted. In the case of refusal, the probability for reaching ketosis over the stay as a consequence of catabolic metabolism is also high [194], but less controllable and of unclear therapeutic relevance. Moreover, fundamental therapeutic aspects, such as the renunciation of resuscitation or the immediate switching to a supportive care setting in the case of acute deterioration, should be addressed early if they were not already mentioned in the ACP documentation. In this context, the withdrawal and withholding of life-supporting treatment, including ASDs, as a possible measure of LOT should also be addressed [188–190]. A re-evaluation of the health condition, therapeutic approaches, and further diagnostic or therapeutic steps should be performed at regular intervals and discussed with the patient, their caregivers or their healthcare agents where appropriate. If any doubts exist as to the medical ethical tenability of the chosen therapy regimen and the patient's advance directive, a third neutral party, such as an ethics committee should be consulted. In addition, the well-being and possible illness-specific consequences of caregivers should be addressed during and after therapy [195].

The approximate mortality rate for RSE and SRSE in unrestricted therapy settings is 35–40% [12, 196–198], supporting such an outcome in a far higher proportion of patients with ACP, undergoing LOT or in a PCS. In the case of a continuing refractory course or an acute deterioration of the health state, palliative sedation and analgesia using BZDs, propofol, or morphine should be considered within the setting of a dying patient, with the aim of anxiolysis, freedom from pain and convulsive seizures, and mitigation of respiratory distress [18, 19].

5 Conclusion

Refractory SE in patients undergoing LOT or in a PCS represents a difficult challenge for modern clinicians, intensivists and epileptologists. The evidence for the use of ASDs and other minimally or non-invasive therapy options in RSE

beyond that in current guidelines is low, but several effective and well-tolerated therapies are available that should be considered in this patient population. In particular, newer third- and fourth-generation ASDs such as LCM, TPM, BRV and PER seem to be a feasible escalation option for the treatment of RSE in patients undergoing LOT or in a PCS. These drugs can be rapidly uptitrated and applied orally, via nasogastric tube, and two of them are also available as an intravenous solution. In addition, the KD represents a practicable non-invasive therapy option that may be considered individually. More so than in any other population, advance care planning, advance directives, and medical ethical aspects have to be considered carefully before the initiation of therapy. Furthermore, the determination of no further escalation of therapy with ASDs, or their discontinuation in the context of terminal care, has to be considered and re-evaluated on a regular basis depending on the individual's clinical course and the ACP or directives.

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