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REVIEW

Continuous Infusions of IV Anesthetizing Antiseizure Medications for the Treatment of Refractory Status Epilepticus: A Critical Review

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Abstract

Purpose of Review To enhance awareness of practice guidelines for the treatment of established convulsive status epilepticus (CSE) and to recommend their use wherever possible. To critically review the literature on the use of standard non-anesthetizing antiseizure medications (ASMs) versus continuous infusion anesthetizing drugs (CIVADs) for the treatment of refractory SE (RSE).

Recent Findings A 2026 French national study reported a hospitalization rate for SE of 15.6/100,000 persons and a 1-year mortality rate of 36%. Many new studies, including a randomized, controlled trial (RCT), support the American Epilepsy Society's treatment guideline for children and adults with established CSE. Numerous new reports show that full, weight-based doses of benzodiazepines should be administered per CSE guidelines to avoid patient harm. Multiple observational studies have documented benefits and harms with the use of CIVADs in 3rd phase treatment of convulsive RSE and non-convulsive SE (NCSE) with coma. Although many clinicians favor CIVADs, equipoise exists as to whether standard ASMs might suffice as the initial treatment of convulsive RSE for many patients. Convulsive RSE often evolves to NCSE with coma, and both are commonly treated with CIVADs despite the lack of class I RCTs comparing CIVADs to standard non-anesthetizing ASMs. Continuous EEG monitoring is highly desirable, but not available in many countries and hospitals, for diagnosis and to assist with CIVAD dosing and weaning decisions. Many healthcare disparities exist globally in the diagnosis and treatment of SE. Two new class I RCTs are underway, as are new clinical practice guidelines.

Summary Prompt first-phase treatment of CSE should include full doses of an IV or IM benzodiazepine. Recommended second phase treatment is a full loading dose of IV levetiracetam, fosphenytoin, or valproate (or if none of these are available, phenobarbital) per evidence-based guidelines. For convulsive RSE, third-phase treatment could include IV bolus fosphenytoin, lacosamide, levetiracetam, or valproate, or IV infusion ketamine, midazolam, pentobarbital (thiopental, in Europe), or propofol based on the clinical situation, the ASM used in the second phase, drug and intubation availability, availability of continuous EEG monitoring, and the health care provider's experience and comfort using these non-anesthetizing or anesthetizing drugs. Lacosamide and the CIVADs have shown efficacy in convulsive RSE. CIVADs are often used in the treatment of nonconvulsive RSE with coma which may occur from the onset or may follow convulsive RSE. Complete or marked reduction of electrographic seizure patterns on EEG is probably a useful efficacy outcome indicating that it is reasonable to begin weaning CIVADs. A large, prospective, randomized trial of standard ASMs versus CIVADs for the treatment of convulsive RSE is needed.

Keywords Status epilepticus · Convulsive · Non-convulsive · Ketamine · Midazolam · Propofol · Pentobarbital · Thiopental

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Introduction

Status epilepticus (SE) is a medical emergency that requires urgent and accurate diagnosis and guideline-driven treatment, whenever possible in global healthcare settings. Several types of SE occur. Some are mild with little to no impairment of consciousness whereas non-convulsive SE

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with coma and convulsive SE have high morbidity and mortality rates. This review first briefly covers the ideal guideline for the initial treatment of convulsive SE and then provides more details on the approaches and controversy in the use of continuous infusion anesthetizing drugs to treat refractory status epilepticus.

Status Epilepticus

Definition and Classification

The International League Against Epilepsy published a definition and a classification of status epilepticus (SE) [1].

SE is, *"a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t_1). It is a condition, which can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures. This definition is conceptual, with two operational dimensions: the first is the length of the seizure and the time point (t_1) beyond which the seizure should be regarded as 'continuous seizure activity' The second time point (t_2) is the time of ongoing seizure activity after which there is a risk of long-term consequences. In the case of convulsive (tonic-clonic) SE, both time points (t_1 at 5 min and t_2 at 30 min) are based on animal experiments and clinical research."* [1].

This classification of SE is based on 4 axes: semiology (with and without prominent motor signs), etiology (known and unknown causes), EEG patterns and features, and age (neonatal, infancy, childhood, adolescence, adulthood, and old age) [1]. A simple classification of the common types of SE based only on the first axis is convulsive SE (CSE), defined as overt convulsions lasting > 5 min or 2 + back-to-back tonic–clonic seizures without full return of consciousness between them, nonconvulsive SE (NCSE) which includes continuous absence, focal sensory, or focal impaired awareness seizures lasting 10 or more minutes, myoclonic SE, and focal motor SE [2]. This updates older definitions [3, 4].

Stages

The first stage, called developing status epilepticus, is repeated seizures leading up to SE. The second stage is established status epilepticus (ESE), defined as SE lasting more than 5 minutes at which time therapy should begin. The third is refractory status epilepticus (RSE) which is continued SE due to failure of 2 adequately dosed ASMs in different drug classes (e.g., a benzodiazepine and phenytoin). The fourth stage is super-refractory status epilepticus (SRSE), defined as SE persisting despite > 24 h of the use of continuous infusion anesthetizing drugs (CIVADs) [5].

Epidemiology

In 2026, the Italian Pediatric SE Group's multicenter study noted that 74% of children with SE had a history of epilepsy [6]. Of the 790 children with epilepsy and SE, 66% had a confirmed or presumed genetic etiology [6]. While epilepsy may be a common etiology of SE in children, several other etiologies of SE are common in adults (see below). In an Australian study, SE was the first seizure presentation in 20% of 1,278 patients [7]. When the first seizure is SE there is a substantially higher risk of death [7]. A 2026 French study of over 118,000 SE patients reported that the hospitalization rate for SE was 15.6/100,000 persons, and that the in-hospital and 1-year mortality rates were 22.9% and 36.0%, respectively [8]. A study of 38,000 patients aged < 1 to > 80 years found a 3-year mortality of 25% after a first episode of SE [9]. The highest mortality occurred in patients receiving prolonged mechanical ventilation or those not admitted to an intensive care unit (ICU) [8]. Other factors associated with mortality are older age, longer duration of SE, higher Status Epilepticus Severity Score (STESS), cardiac arrest as etiology, tumors, cardiovascular disease, infectious disease, respiratory disease, > 2 days of mechanical ventilation, and NCSE with coma [8–16]. In the US, deaths from SE have been rising: age-adjusted mortality rates were stable between 1999 and 2007, followed by an increase until 2020 [16]. The rise from 2007 to 2020 began before the definition of SE was revised in 2015, so the new, more liberal definition of SE does not appear to explain the increased mortality rate [16]. In that interval, 32,174 adult Americans had SE-related deaths; most occurred in medical facilities (83.7%) [16]. Taken together, these statistics indicate a need for better education on, and treatments for, status epilepticus.

Convulsive Established Status Epilepticus

The American Epilepsy Society (AES) published a clinical practice guideline on the treatment of convulsive ESE in children in adults [17]. Ratings of the levels of evidence for this guideline were based on an earlier modification of the 2017 American Academy of Neurology Clinical Practice Guideline Process Manual [18]. Older SE guidelines exist [4, 19, 20]. In the SE literature the terms "first-line," "second-line," and "third line treatment are used frequently, but this could erroneously suggest to readers that "first line"

therapy has superior efficacy when the intent was merely to designate a position or step in the treatment algorithm. To avoid confusion, we propose the term "first phase" etc. for this purpose.

First Phase Treatment

For the 1 st phase of treatment of convulsive ESE (CSE), 4 mg of lorazepam i.v., 10 mg or midazolam i.m., or 10 mg of diazepam i.v. is recommended for adults weighing over 40 kg (Table 1) [17]. This was supported by several randomized controlled trials (RCTs) [21–24]. Lorazepam may be superior to diazepam [22, 25]. Diazepam is a more lipid-soluble benzodiazepine (BDZ) than lorazepam, resulting in faster blood-brain barrier penetration, but diazepam subsequently redistributes back out of the brain into adipose tissue resulting in a short, 2–4 h, duration of effect on the brain [3, 26]. A midazolam autoinjector, similar to the one used in the RAMPART study [21], was approved in 2022 for the treatment of SE in the US, but is not yet marketed. Some US physicians use the intranasal diazepam or intranasal midazolam devices when i.v. access and i.m. benzodiazepines are not available, but neither are approved by the FDA for status epilepticus. They are only approved for the treatment of acute repetitive seizures (clusters) and have not undergone RCTs in 1 st phase treatment of CSE. If an intranasal device is used to treat SE, healthcare providers should probably use appropriate age-based and weight-based dosing [2, 27].

Despite guidelines to use full doses of BDZs, multiple research studies have shown that the vast majority of children and adults with SE are underdosed [28–30]. For example, even in the class I randomized, controlled Established Status Epilepticus Treatment Trial (ESETT) midazolam and lorazepam doses were lower than guideline recommended in >75% of the 460 subjects [31]. Up to 3 negative outcomes may occur when adults and children are given BDZs that do not adhere to SE guidelines.

1. Providers may prescribe lower BDZ doses due to the mistaken belief that it will reduce the risk of respiratory depression. In fact, the opposite is true: uncontrolled SE is more likely than are BDZs to cause respiratory depression. Indeed, the PHTSE Class I RCT for prehospital SE showed that patients randomized to placebo had more than twice the rate of respiratory dysfunction than those who received lorazepam or diazepam [22].
2. Low dose BDZs are less effective at stopping SE than full dose BDZs [15, 32]. The Sustained Effort Network for treatment of Status Epilepticus (SENSE) observational registry found that BDZ doses were lower than recommended in >75% of refractory CSE and NCSE adults compared to non-refractory patients ($p<0.001$) ($n=1049$) [30]. In that study, the time from CSE onset to 1 st treatment was 30 min, time from NCSE onset to 1 st treatment was 2.5 h, and the use of BDZs, and higher total dose of ASMs, used in 1 st phase produced a shorter time to CSE and NCSE control [30]. Among the 996 patients in the SENSE registry, 54.7% progressed to RSE in whom there was a greater likelihood of deviation from treatment guidelines ($p<0.001$) [33]. In an Italian observational study of 1374 episodes of pediatric CSE, non-adherence to treatment guidelines [17, 20] or MDZ infusion doses of ≤0.2 mg/kg/h were associated with an increased chance of refractoriness and length-of-stay [32].
3. Time delays in the delivery of BDZs to patients with SE are associated with greater adverse outcomes, including death. The Pediatric Status Epilepticus Research Group (PSERG) has studied delays in SE treatment with both BDZs and standard ASMs. A PSERG multicenter study of refractory CSE found that the 2/3 of children who received delayed 1 st phase BDZ treatment had greater odds of death and need for continuous infusion anesthetizing ASMs, longer duration CSE, and more frequent hypotension [34]. Intermittent convulsive RSE and onset of convulsive RSE outside the hospital were each associated with longer delays to administration of both the first BDZ and the first standard ASM [35]. One PSERG study found that the first dose of both a BDZ and standard ASM were given 30 and 69 min after the onset of SE in children [36]. Additionally, children did not receive more timely treatment if they had a prior history of

Table 1 AES guideline for convulsive established status epilepticus [17]

First phase:
i.m. midazolam 10 mg for body weight >40 kg (5 mg for 13–40 kg) single dose, OR
i.v. lorazepam 0.1 mg/kg/dose, max: 4 mg/dose, may repeat once, OR
i.v. diazepam 0.15–0.2 mg/kg/dose, max: 10 mg/dose, may repeat once
OR if none of the above are available, give:
i.v. phenobarbital 15 mg/kg single dose, OR
rectal diazepam 0.2–0.5 mg/kg, max 20 mg single dose, or nasal or buccal midazolam
Second phase:
i.v. fosphenytoin 20 mg PE/kg, max 1500 mg PE, single dose; up to 150 mg/min (may instead be given i.m), *OR*
i.v. valproic acid 40 mg/kg, max 3000 mg, single dose, OR
i.v. levetiracetam 60 mg/kg, max 4500 mg, single dose
OR if none of the above are available, give:
i.v. phenobarbital 15 mg/kg, single dose

PE = phenytoin equivalent

epilepsy; a history of SE was associated with more timely administration of a rescue medication yet it was only given in 1/3 of cases [36].

New research on 1st phase treatment includes the pediatric Ket-Mid Study [37]. This RCT included 144 children aged 0.5–16 years assigned to receive a single dose via i.v. push of MDZ 0.2 mg/kg alone versus MDZ 0.2 mg/kg plus ketamine (KET) 2 mg/kg IV [37]. Cessation of CSE by the 5-minute point occurred in 76% of children receiving combined MDZ and KET and 21% of those receiving MDZ alone (RR 3.7) [37]. The ketamine + midazolam group also experienced fewer intubations and fewer repeat MDZ boluses. A limitation of this study is that almost half the children had a febrile etiology of their SE, so further studies are needed to confirm these findings [37].

Second Phase Treatment

For 2nd phase of treatment of CSE, i.v. loading doses of fosphenytoin (FOS) 20 mg PE/kg, valproate (VPA) 40 mg/kg or levetiracetam (LEV) 60 mg/kg are recommended for children and adults (Table 1) [17]. After AES Guideline publication, additional studies on these ASMs have been conducted. The ESETT study was a U.S. National Institutes of Health funded, blinded RCT of 384 patients aged 1–95 years with BDZ-resistant CSE [38]. Treatment was i.v. loading doses of FOS 20 mg PE/kg, LEV 60 mg/kg, or VPA 40 mg/kg. Efficacy was the same for LEV (47%), FOS (45%), and VPA (46%) (N.S.) (level B, likely effective), and there were no differences in level of consciousness or major safety events [38].

One class I study reported that the initial clonazepam 1–2 mg i.v. dose controlled pre-hospital CSE equally well in adults who later received either placebo or levetiracetam 2500 mg [39]. A class II study of older adults aged > 60 years found that after initial 4–6 mg lorazepam dose, control of CSE was no different between i.v. loading doses of LEV 20–25 mg/kg and VPA 20–25 mg/kg [40]. Two class III open-label RCTs in children with CSE found that i.v. loads of LEV 40 mg/kg and PHT 20 mg/kg are possibly equally effective in terminating CSE (Level C) [41, 42]. Other smaller studies on 2nd phase treatment of children and adults with CSE have been completed [43–45]. Taken together, the class I ESETT RCT in adults and children, 2 large class II RCTs in adults, 2 class III pediatric open-label studies, and others have confirmed no major differences between LEV, PHT/FOS and VPA in controlling established CSE. These support the 2016 AES Guideline [17].

Convulsive Refractory Status Epilepticus

Epidemiology

A US Veterans Affairs trial showed that the first ASM worked in 55.5%, the second ASM in 7.0%, and the third ASM worked in only 2.3% of adults with CSE [23]. In children, the second ASM appears less effective than the first, and there are no data about the third ASM [17]. Later studies found that RSE develops in 23–55% of patients with SE, causes death in 15–39% of adults (a lower rate in children), and leads to a return to baseline neurologic status in a minority of patients, longer hospital stays, and a need for rehabilitation in many patients [33,46–52]. A Korean study of new-onset SE determined that 30-day and 1-year mortalities were 1.8% and 4.6%, respectively, for children and 10.2% and 30.3%, respectively, for adults [53]. It included all potential etiologies of SE, with only 5% attributed to anoxic brain injury. Of the 33,814 patients, 33.2% of children and 17.6% of adults progressed to RSE requiring continuous infusion anesthetizing drugs (CIVADs). New neurologic disabilities occurred in 10.7% of all patients, but the greatest risk of disability was in children aged 5 to 9 years (21.3%) [53]. New, treatment-resistant epilepsy occurred in 0.8% overall [53]. Factors predictive of mortality in children and adults were old age, the presence of acute etiology, and RSE [53]. Note that SE, RSE and NCSE following cardiac arrest are very treatment resistant, have been excluded from almost all studies, and are not considered further here.

Third-phase Treatment

Continuous Infusions of Anesthetizing Drugs

For 3rd phase treatment of convulsive RSE clinicians more often use CIVADs, e.g., ketamine, midazolam, pentobarbital (or, in Europe, thiopental), or propofol than use a second standard ASM due to a belief that CIVADs will lead to faster cessation of the SE. Unfortunately, Class I prospective, RCTs comparing the benefits and harms of CIVADs to the efficacy and adverse events associated with a second non-anesthetizing ASM have not been completed [17]. As a result, only retrospective, uncontrolled, observational studies are available to provide some guidance.

Harms of CIVAD Use Class III studies have identified an association between CIVAD treatment of RSE with poorer outcomes (as measured by Glasgow Outcome Scale [GOS] or modified Rankin scale [mRS]) and a greater risk of death [54]. Two studies found that CIVAD use was associated with a 3-fold risk of death, 2-fold risk of poorer outcome, and 4-fold increased incidence of infection compared to

standard ASMs, even when correcting outcome determinants using propensity score matching [55, 56]. Another study of CIVADs found a 7-fold relative increased risk of new disability, a 9-fold increased risk of mortality, a 4-fold increased risk of infection, and a 1-week prolongation of hospital stays compared to standard ASMs [57]. One study found that CIVAD versus standard ASM use differed about 3-fold between Swiss and Boston hospitals and that CIVADs were associated with longer hospitalizations, but not with greater mortality, and was more commonly used in patients with higher Status Epilepticus Severity Score (STESS) [58] and younger age [59].

Benefits of CIVAD Use A German retrospective study examined older adults (median age 70 years) with convulsive RSE (44.2%), focal impaired consciousness RSE (36.4%) and NCSE (19.5%) who were treated in 2001–2015 with a median of 2 CIVADs (one was most commonly propofol) [60]. Those who received CIVADs within the first 48 h of RSE onset ($n=53$) had a better outcome (mRS score < 3 or complete recovery) at 12-week follow-up, a lower chance of progression to thiopental use and of having burst-suppression induced, and a shorter duration of RSE compared to patients who received CIVADs later ($n=24$) [60]. A confounder was that more than three times as many patients in the early CIVAD group had CSE (56.6%) than in the late group (16.7%) [60]. Two retrospective studies on patients treated with CIVADs for RSE [61] and, as second-phase, for CSE [62] (there were no comparisons to standard ASMs) reported that shorter duration and higher dose therapeutic coma was associated with fewer in-hospital complications and shorter durations of mechanical ventilation and hospital stay [61, 62]. A third study analyzing 111 adults treated at a Swiss hospital for RSE found that the doses of CIVADs had to be increased in 57% due to lack of SE control.63 Even though subjects with anesthetic dose escalation in that study had higher morbidity than those without CIVAD dose increases, they had decreased odds of in-hospital death, and the survivors had similar functional outcomes [63].

Summary on Benefits/Harms of CIVADs These retrospective studies provide conflicting data on the harms and benefits associated with the use of CIVADs compared to the use of additional standard ASMs. A systematic review in 2024 concluded that the data from the original studies included in the review were so heterogeneous that no definitive conclusion could be reached on the best first ASM to select for the treatment of convulsive RSE [64]. Future research will hopefully identify RSE patient subgroups that are more likely to experience benefits, and less likely to have negative outcomes, when treated with CIVADs.

Newer Research on CIVADs for Convulsive RSE The MORSE CODe study of 386 adults compared outcomes in patients with convulsive RSE that received CIVADs in high-income versus low–middle-income countries and found that midazolam and propofol infusions had equally good outcomes [65]. A recent retrospective study compared 5310 patients who received midazolam to 2136 patients who received propofol infusion on the day of RSE onset [66]. After propensity score matching for premorbid health conditions, patients receiving MDZ had decreased risk of mortality at 30 days (but not at time of maximal follow-up), and reduced hazards of lactic acidosis, rhabdomyolysis, hypertriglyceridemia, tracheostomy, gastrostomy tube placement and mechanical ventilation, compared to those who received PRO [66]. A SENSE retrospective study of adult cases seen in 2011-15 who received anesthetic drugs as either 1 st -phase or 2nd -phase treatment was performed to determine if early anesthesia improved prognosis. Fifty five patients with CSE and NCSE in coma received early anesthesia and were compared to 994 who either received CIVADs as 3rd -phase or not at all [67]. Those receiving early anesthesia had deeper consciousness impairment and more severe SE semiology, but mortality, functional outcome, SE cessation rate and durations of SE and hospital stay were similar between the groups [67].

A study on the treatment of RSE in neonates and children at a university pediatric hospital showed that ketamine had efficacy in three-fourths of cases [68]. A 2024 systematic review of ketamine in pediatric RSE indicated that it ended RSE in 51% of the children with no significant side effects [69]. A 2025 systematic review of 10 studies involving ketamine for treatment of SE found efficacy in 59% of adults and 50% of children, but with wide variability of the KET dose used and the use of concomitant CIVADs [70]. Furthermore, a 2026 systematic review/meta-analysis of adult RSE and SRSE found that treatment with i.v. ketamine after 3 or more ASMs (including infusions of MDZ in all, PRO, and phenobarbital) the pooled proportion of seizure cessation was 64% [71].

Practice variation between hospitals leads to differences in treatment practices. For example, a review of SE treatment protocols submitted by 256 epilepsy centers for accreditation by the US National Association of Epilepsy Centers disclosed that only 66% of protocols specified goal times for ASM administration, that doses were below those

in the AES Guideline, and that CIVAD therapy was outlined in 61% of the protocols (of which recommended doses were specified 18% of the time for ketamine, 52% for midazolam, 45% for propofol, and 41% for pentobarbital [72].

Non-anesthetizing ASMs

Standard, i.v. non-anesthetizing ASMs are often used as initial 3rd phase therapy for convulsive RSE. Novy and colleagues reported that escalating treatment with a standard ASM terminated convulsive RSE in more than one-half of their patients, avoiding the need to progress to CIVAD therapeutic coma [50]. Similarly, a Class III study of lorazepam followed by FOS, LEV, and VPA found that by the time all three were used sequentially, CSE was controlled in 92% of patients, thereby avoiding the need to use CIVADs [48]. In the SENSE registry [30], 287 of 545 (52.7%) patients with RSE had good treatment outcomes (mRS score unchanged or ≤2) correlated with lower SE severity, lack of intubation (on CIVADs), adequate first-phase BDZ dose, absence of acute etiology, and shorter durations of status epilepticus and hospitalization (all $P<0.001$) [33]. Noted that in the SENSE registry, the doses for LEV, FOS, and VPA were all lower than in the AES Guideline [17] and the ESETT study [38]. These three studies suggest that the use of CIVAD coma might be avoided in favor of another standard ASM in many patients, particularly when guidelines are correctly followed for dosing and timing of 1 st phase and 2nd phase treatments.

Limitations with all retrospective CIVAD and standard ASM studies for convulsive RSE are that they probably had selection bias because patients receiving CIVADs may have been more ill or had more refractory CSE, and that ASM timing and dosing were not blinded, randomized, or controlled [73]. For example, a study examining clinical features affecting treatment selection and subsequent outcome found that CIVADs were chosen more often in patients with high ictal burden, fewer comorbidities, and a low Glasgow Coma Scale score [74].

After lacosamide (LCM) was marketed in Europe and the US, several uncontrolled studies were reported in which it was used as a 3rd phase treatment for convulsive RSE. This led one of us (DGV) to propose in 2012 that the AES develop new guidance for the treatment of RSE. In late 2020 the "Treatment of Refractory Convulsive Status Epilepticus: A Comprehensive Review by the American Epilepsy Society Treatments Committee" was published [73]. It determined that LCM is possibly effective at stopping convulsive RSE in children and adults (Level C; 2 Class III and 14 Class IV studies), but that insufficient evidence of efficacy existed for the other IV ASMs: brivaracetam, FOS, ketamine, LEV, midazolam, pentobarbital (thiopental, in Europe), propofol, and VPA [73]. Pharmacologic information on the standard ASMs and CIVADs used for 3rd phase treatment of convulsive RSE is shown in Table 2 [73]. Separately, the TRENdS single-blinded, prospective, RCT compared LCM versus FOS in the treatment of nonconvulsive seizures in adult intensive care patients who were undergoing cEEG (more severe cases of NCSE were specifically excluded [75]. One initial dose of LCM 400 mg ($n=30$ patients) was non-inferior to FOS 20 mg PE/kg [75]. This was the first prospective RCT of ASMs for nonconvulsive seizures and also the first to use cEEG findings as a primary efficacy endpoint [75].

By the early 2020 s, evidence was mixed regarding whether a CIVAD or a second standard ASM should be initiated immediately after failure of properly dosed second-phase treatment [59, 62, 73, 76]. Since the AES convulsive RSE review was published, 3 studies of non-anesthetizing ASMs have been reported. A new class IV study on 2nd phase treatment for ESE compared LCM, LEV and VPA and reported that all were equally effective [77]. A Japanese observational study showed that LCM as the 2nd -phase drug (after an initial BDZ) was associated with a lower rate of poor neurological status at discharge compared to LEV and that the in-hospital mortality was similar for these ESE patients receiving LCM or LEV.78 Thirdly, a dosing study in patients with RSE and SRSE found that phenobarbital has high inter-individual and inter-episode pharmacokinetic variability resulting in low attainment of desired plasma concentrations, thus underscoring the need for therapeutic drug monitoring of phenobarbital in clinical practice [79].

Factors contributing to the desire to use a standard ASM as opposed to a CIVAD as 3rd phase treatment for RSE comes from the well-known adverse events associated with prolonged infusion anesthesia: infections, hypotension requiring pressor support, cardiac depression, propofol infusion syndrome (especially in children), ileus, immunosuppression with barbiturates, and post-weaning delayed extubation and delirium [73, 80].

Non-convulsive Status Epilepticus

The use of CIVADs to treat NCSE can be clinically challenging. It is not guided by either the guidelines for treating convulsive ESE or the data presented above for convulsive RSE. The evidence guiding CIVAD use in NCSE unfortunately is limited and heterogeneous [80]. The intensity of treatment is, in part, suggested by the severity of the NCSE. For example, it is clinically reasonable to consider continuing CIVAD treatment for the subtle or electrographic-only NCSE with coma that

Table 2 Parenteral antiseizure medications for refractory status epilepticus

Medication	Loading dose (i.v.)	Maintenance Dose (i.v.)	Approximate plasma $t_{1/2}$ (hr)	Plasma level (mcg/mL) ***	Some important considerations
Brivaracetam (BRV)	unknown	11–19 kg = 2.5 mg/kg bid; 20–49 kg = 2 mg/kg bid; 50 + kg = 100 mg bid (age 4 + yr); 100 mg bid (adult)*	9	-	Some DDIs
Fosphenytoin (FOS)	20 mg PE/kg at: Children: ≤2 mg PE/kg/min. Adult: ≤150 mg PE/min. Max 1500 mg PE	Children: 4–8 mg PE/kg/day (up to 300 mg PE ages 6–17) divided bid - tid. Adult: 300–600 mg PE/day divided bid - tid.	22 in adults	10–25	FOS may be given i.m. Lower risk of thrombophlebitis and hypotension than with PHT. ECG monitoring advised. May cause rash, Stevens Johnson Syndrome. DDIs
Ketamine (KET)	1–2.5 mg/kg	3–10 mg/kg/hr**	2.5–3	-	Combine with BDZ. Avoid in neonates and in 3rd trimester of pregnancy
Lacosamide (LCM)	5–10 mg/kg over 15–30 min^{+} (FDA approved "loading dose" is 200 mg in adults)	13 mg/kg/day divided bid (children); 200 mg bid (adult)*	15	4–12	Atrial arrhythmia; 1 st, 2nd and 3rd degree heart block. Rarely: ventricular arrhythmia, death. Reduce dose in renal or hepatic impairment
Levetiracetam (LEV)	60 mg/kg over 15 min (max 4500 mg)	21 mg/kg bid (< 6 mo), 25 mg/kg bid (0.5–4 year), 30 mg/kg bid (4–16 year), 1500 mg bid (adult)*	7	20–50	Reduce maintenance dose in renal impairment
Midazolam (MDZ)	0.2–0.5 mg/kg	0.1–4 mg/kg/hr**	Initially = 1–4.5 (child), 2–7 (adult); Prolonged ≤ 24	variable	Clearance is fastest in infants and slows with prolonged use, tachyphylaxis
Pentobarbital (PTB)	5–15 mg/kg at max 50 mg/min	0.5–5 mg/kg/hr**	15–22	-	Hypotension, ileus, immune suppression, adipose tissue accumulation
Propofol (PRO)	1–2 mg/kg bolus every 3–5 min, max 10 mg/kg	1–15 mg/kg/hr initially, then max 5 mg/kg/hr**	Initially = 0.67, Prolonged = 4–7, > 10 days = 24–72	-	Children: avoid or use only briefly due to risk of PRIS
Thiopental (THP)	2 mg/kg at max 50 mg/min	0.5–5 mg/kg/hr**	3–22	-	Hypotension, ileus, immune suppression, adipose tissue accumulation
Valproate sodium (VPA)	40 mg/kg over 10–60 min (max 20 mg/kg/min)	5–15 mg/kg every 6 h starting 30 min after loading. Max 60 mg/kg/day total*	9–16	50–100+	May cause hyperammo-nemic encephalopathy, pancreatitis, hepatoxicity, DDIs

Key: $^{+}$ Theoretical loading dose, but ventricular and atrial arrhythmias are a concern. * Maximum FDA-approved maintenance dose for ambulatory epilepsy patients, ** may be titrated to desired EEG patterns, *** common steady state serum concentrations observed in ambulatory epilepsy patients. *BDZ* = benzodiazepine, *bid* = twice daily, *DDI* = drug-drug interaction, *ECG* = electrocardiogram, max = maximum, *PHT* = phenytoin, *PRIS* = propofol infusion syndrome, *tid* = three times daily

often follows treated convulsive RSE. Certainly, refractory NCSE with coma has been shown in many studies to have a poor prognosis for outcome [14]. It is difficult to discern whether the cause of the coma is the SE itself, the underlying pathology, or both. This makes the decision to escalate or wean CIVAD doses in individual NCSE with coma patients both complicated and uncertain [80]. Cases of NCSE with no-little alteration of consciousness may not require CIVAD therapy, and may be best treated with standard, non-sedating ASMs [81]. Recent, detailed reviews of the various types of NCSE, with and without coma, exist [80, 82].

Super-refractory Status Epilepticus

SRSE leads to an in-hospital mortality of 24.1% and moderate to severe disability in a large proportion of patients [83]. In a 2023 systematic review, treatment of SRSE with ketamine, phenobarbital, other barbiturates, ketogenic diet, and vagus nerve stimulation did not improve cessation of SE or in-hospital survival [83]. A full review of SRSE is beyond the scope of this chapter, so readers are referred to our recent publication [2]. A new study at one center reported that ketamine given as an initial 2–3 mg i.v. bolus followed by CIVADs (sometimes along

with MDZ or PRO) controlled SRSE in 58% of patients, and that elevated whole-blood inflammatory indices were associated with treatment failure and mortality [84]. Further work is needed to confirm the latter findings.

CIVAD Dose Monitoring and Weaning

The decision to maintain or wean the dose of CIVADs is often guided by clinical observation and, where available, the findings of continuous EEG (cEEG) monitoring. For decades there has been controversy as to whether the presence of an EEG burst-suppression pattern can guide CIVAD dosing and weaning. The American Clinical Neurophysiology Society's 2021 standardized terminology defined burst-suppression as having 50–99% of the recording characterized by attenuation/suppression [85]. There are problems using burst-suppression as a clinical guide. Firstly, burst-suppression cannot always be either achieved or maintained in a stable pattern using CIVADs [80]. Secondly, ketamine alone does not produce a burst-suppression pattern; it produces a mix of gamma and delta waves [80]. Thirdly, as summarized by Fisch et al. [86] several studies have not demonstrated that the EEG burst-suppression pattern has clinical utility in RSE. This conclusion was recently supported by the same group in a study of 147 RSE patients (45 of whom had an anoxic etiology for RSE) [86]. Three burst-suppression categories were specified: complete (≥50% of EEG epoch shows attenuation/suppression), incomplete (20–49%), and none. They found that only one-fifth of patients met the ACNS criteria for burst suppression [86]. Most importantly, they determined that a burst-suppression pattern did not demonstrate a greater chance of persistent seizure termination, in-hospital survival, or return to premorbid function [86]. In the subgroup of patients with anoxic RSE, however, burst-suppression was associated with better seizure termination and survival [86]. A pragmatic approach is to not use the EEG burst-suppression pattern as a guide, but rather is to dose CIVADs in order to suppress most clinical and electrographic seizures, often tolerating a few brief seizures each day, in an attempt to reduce the chance of complications that occur with high-dose CIVAD anesthesia.

An EEG rating scale called the 2HELPS2B score was published in 2017 to assist in determining the probability that an inpatient is having electrographic seizures [87]. The 2HELPS2B score assigns a point value for each of six potential EEG patterns, and the total score corresponds to the probability that the patient suffers from seizures (Fig. 1). The patterns are brief ictal rhythmical discharges (2 points), presence of lateralized periodic discharges, lateralized rhythmic delta activity or bilateral independent periodic discharges (1 point), prior seizure (1 point), sporadic epileptiform discharges (1 point), frequency > 2 Hz for any periodic or rhythmic pattern (1 point), and presence of "plus " features (superimposed, rhythmic, sharp, or fast activity) (1 point) [87]. A recent single-center case-control study of 102 nonanoxic adult patients treated with CIVADs for RSE found that weaning of the anesthetics failed in 35% of cases [88]. Failure to wean was associated with a higher STESS, super-refractory SE, longer CIVAD therapy before weaning, more CIVADs at the time of weaning, breakthrough seizures before the wean attempt, and electrographic seizures during the hour prior to the attempt. The authors devised a modification of the 2HELPS2B score and showed that it was somewhat more accurate that the original score; a modified score ≥ 3 had a 95% specificity for failure to wean [88].

Surveys in Europe and other countries regarding physician preferences for the duration of CIVAD therapeutic coma have shown substantial variability. As reviewed by Fisch et al., most clinicians reported that they maintain CIVADs for the first 24–48 h in convulsive RSE before attempting weaning [80]. Interestingly, an American study reported that a first trial of CIVADs for a longer duration (27.2 vs. 15.6 h) was associated with a higher risk of seizure recurrence following the first attempt to wean CIVADs [61]. Likewise, the MORSE CODe study reported that longer CIVAD treatment was associate with higher rates of breakthrough seizures, but that longer cEEG monitoring was associated with shorter duration of CIVAD therapeutic coma [65]. It is possible that longer duration initial CIVAD administration was given to patients appearing to have more severe cases of convulsive RSE.

Summary

A single, arbitrary time duration for treatment of RSE with CIVADs has not been established. Some findings in cEEG monitoring appear to be useful as guidance for weaning CIVADs. An EEG burst-suppression pattern does not appear to be a useful guide for the use of CIVADs. In contrast, the

Total Score	0	1	2	3	4	5	>6
Probable risk of seizure (%)	5	12	27	50	73	88	>95

Fig. 1 2HELPS2B score. The figure shows the total scores corresponding to the probable risk that an EEG is consistent with seizures

new modified 2HELPS2B score may prove to assist in the weaning process if replicated in future research studies. Given the many adverse effects of CIVADs, and the limited availability of cEEG instruments, it is reasonable to use the lowest doses and shortest duration of CIVADs, guided by clinical factors and cEEG findings. Therefore, while many healthcare providers report not weaning CIVADs for 24–48 h, we believe that if cEEG shows no seizures or only anesthetic-induced EEG patterns then weaning should be considered after less than 24 h. A reasonable approach is to dose CIVADs to suppress most clinical and electrographic seizures and allow a few, brief seizures each day.

Healthcare Disparities

Large healthcare disparities in SE epidemiology, diagnosis, and treatment exist globally. Compared to high income countries, low-middle income countries (LMIC) experience: a higher mortality rate (42.6%) [89], higher variability of diagnostic and treatment practices dictated by availability of medications and expertise [89], a desire for improved training [90], under-dosing of first-phase benzodiazepines [90], use of older ASMs like phenobarbital, PHT and VPA [89, 90], and general lack of access to cEEG monitoring [89, 90].

Recent studies show substantial SE healthcare disparities in high-income countries as well. One recent US study showed higher mortality rates in Black and Asian/Pacific Islander patients with SE than in White Americans [91]. In a 2026 US study, mortality rates were highest in adults > 65 years of age, among non-Hispanic Black people followed by non-Hispanic White and Hispanic/Latino populations, and in the South United States [16]. In Canada, the availability of cEEG monitoring is highly limited, even at tertiary care centers [92]. Only 9% of Canadian hospitals have and EEG lab, and only 2% offer cEEG monitoring [92].

Areas of Further Research

The National Institutes of Health-funded KESETT study, a Class I RCT (NCT06907173), is underway at 51 sites in the US to examine the role of an adjunctive ketamine bolus during 2nd -phase treatment of patients aged ≥ 1 year with CSE. Patients must have received an adequate dose of a BDZ 5 to 30 min before the study drug and must have ongoing CSE. Patients receive: (1) LEV at 60 mg/kg by iv infusion alone, (2) LEV in combination with ketamine 1 mg/kg iv bolus, or (3) LEV in conjunction with ketamine 3 mg/kg iv bolus. The primary efficacy outcome is CSE termination within 15 min after starting the study drug which is sustained for 60 min without using an additional ASM.

In Denmark, the first RCT to study NCSE is planned. The Fast Acute Sedation at ICU versus High-Dose IV Antiseizure Medication for Treatment of Nonconvulsive SE (FAST) trial aims to compare the effectiveness of rapid sedation versus high-dose IV standard ASMs alone for NCSE refractory to 1 st phase and 2nd phase therapies [93]. Patients will receive either rapid deep sedation for 20 h with propofol, followed by midazolam, or additional high-dose ASMs like LEV, FOS, VPA, LCM, or topiramate (NCT05263674) [93].

Finally, a new status epilepticus clinical practice guideline is underway, funded and conducted by the American Epilepsy Society. This will update and extend the previous AES guideline [17].

Conclusion and Opinion

Prompt first-phase treatment of CSE should include full doses of an IV or IM benzodiazepine. Second-phase treatment is to administer a full loading dose of IV levetiracetam, fosphenytoin, or valproate (or if none of these are available, phenobarbital) per evidence-based guidelines. For convulsive RSE, third-phase treatment could include IV bolus fosphenytoin, lacosamide, levetiracetam, or valproate, or IV infusion ketamine, midazolam, pentobarbital (thiopental, in Europe), or propofol based on the clinical situation, the ASM used in the second phase, drug and intubation availability, availability of continuous EEG monitoring, and the health care provider's experience and comfort using these non-anesthetizing or anesthetizing drugs. Lacosamide and the CIVADs have shown efficacy in convulsive RSE. CIVADs are often used in the treatment of nonconvulsive RSE with coma which may occur from SE onset or may follow convulsive RSE. Complete or marked reduction of electrographic seizure patterns on EEG is probably a useful efficacy outcome indicating that it is reasonable to begin weaning CIVADs. It is our opinion that there is equipoise regarding the question of whether CIVADs should always be the initial choice for third-phase treatment of convulsive SE. There is literature indicating that standard, non-anesthetizing ASMs can be used as the first drug in third phase treatment in some cases of RSE thereby avoiding many of the harms associated with the use of CIVADs. A large, prospective, randomized, controlled trial of standard ASMs versus CIVADs for the treatment of convulsive RSE is needed. Mortality from RSE remains high and healthcare disparities are a global problem. New research is underway.

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  ○ This guideline, though a decade old, has been supported by one randomized, controlled trial and several good observational studies thereby indicating that it remains valid for first phase and second phase treatment of convulsive established SE.

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  ○ Although not a guideline, this comprehensive review was quite exhaustive and determined that lacosamide and the CIVADs were probably effective for convulsive RSE. It and subsequent research report have shown no significant differences in efficacy between midazolam and propofol.

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  ○ The ESETT study set the new standard for a randomized, controlled trial in status epilepticus. It demonstrated equivalence of fosphenytoin, levetiracetam, and valproate sodium in the second phase treatment of convulsive SE. The new, ongoing KESETT study examines the role of one ketamine bolus added to the early treatment of SE.

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Declarations

Competing interests The authors declare no competing interests.

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