

Treatment Options in the Management of Status Epilepticus

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Opinion statement

Status epilepticus treatment involves the use of several pharmacologic compounds, which are conceptually divided into three successive and additional lines of action. Because of their rapid onset of action, benzodiazepines represent the first approach; these are followed by classic antiepileptic drugs that are administered intravenously. In refractory episodes, pharmacologic coma induction with an appropriate anesthetic is advocated. Apart from first-line compounds, the level of evidence for medications used in status epilepticus is extremely limited. It is important to specifically address etiology in order to maximize the impact of the antiepileptic therapy. Fine-tuning of the treatment strategy, mainly regarding the choice of whether to induce coma, should be approached by balancing the benefits of rapid control of the status epilepticus with the risks of adverse effects. Although each status epilepticus episode should be treated as rapidly as possible, it appears advisable to reserve coma induction for those forms, such as generalized convulsive status, that have been shown to present a consistent risk of neurologic sequelae.

Introduction

Status epilepticus (SE), the most common neurologic emergency after stroke, requires multidisciplinary management, including paramedics and nurses, neurologists, emergency specialists, and intensive care unit physicians; at times, pharmacologists and members of other medical specialties (eg, infectious disease specialists or immunologists) complete the team. SE must be treated as soon as possible in order to prevent potentially harmful complications such as functional neurologic and neuropsychological impairment or even death [1–3]. Despite the important impact of SE, to date there is only a relatively low degree of

evidence concerning its pharmacologic treatment, perhaps because of the marked variability of SE forms and the challenges of designing large collaborative trials (including the difficulty of gathering financial support). As a result, past therapy strategies have been relatively heterogeneous. Although in recent years several national and international guidelines have been published, it remains unclear whether these are thoroughly applied and whether they have led to an improvement of SE prognosis. Moreover, it seems important to adapt treatments to the specific circumstances of each patient, in

order to maximize the ratio between efficacy and adverse effects.

This paper reviews pharmacologic agents used in SE treatment and gives some practical suggestions about treatment options and strategies.

General treatment considerations

Seizures (and, if they are prolonged, SE) result from an imbalance between inhibitory neuronal inputs (mostly through GABA_A receptors) and excitatory inputs (predominantly glutamate-mediated, via kainate and AMPA receptors) [1,4]. This characteristic may be viewed as a rationale for beginning SE treatment with benzodiazepines, which are rapidly acting GABAergic agents. However, in ongoing SE, GABA resistance develops progressively, following receptor internalization into the cell and subunit changes; this process leads to a shift toward self-sustaining glutamate-mediated excitotoxicity, resulting primarily from the activation of NMDA receptors. These

changes likely explain both refractoriness to benzodiazepines and excitotoxic neuronal damage.

SE treatment aims at stopping seizure activity and concomitantly preventing complications. First, pulmonary and cardiac functions need to be secured; in parallel, a targeted examination and history-taking must be performed to detect possible SE imitators, such as movement disorders (eg, shivering in the ICU) or psychogenic seizures, which may account for a not-negligible proportion of “convulsions” in the emergency room [5]. Sequential laboratory and neuroradiologic workups are needed to address SE etiology, which may greatly influence the success of specific treatments, including the choice of antiepileptic drugs (AEDs). As a rule of thumb, SE treatment should be performed with the help of electroencephalography (EEG). Prolonged recordings are best, as they not only allow judgments about the efficacy of administered agents but also are required for the diagnosis of nonconvulsive SE (ie, complex-partial SE, absence SE, or SE in coma).

Treatment

Pharmacologic treatment

- It is useful to categorize pharmacologic SE treatment into three steps [2], bearing in mind that, in general, intravenous administration is to be preferred because of the possibility of fast loading. The first treatment line is represented exclusively by benzodiazepines aiming at rapid SE control, the second line by classic AEDs targeting early resistant forms of SE and long-term coverage following anticipated control of SE, and the third line by general anesthetics used for refractory SE. This approach should be not only sequential, meaning that the next step is initiated as soon as the previous one is considered to have failed, but also additional, implying that previous treatment lines should not be discontinued, thus allowing complementary actions thanks to different pharmacodynamic mechanisms. A simple protocol with corresponding timing is proposed in Fig. 1. Awareness of a protocol allows a smooth interplay between different team members (paramedics, emergency or ICU team, neurologists) and probably reduces wasted time during emergency management. However, every protocol, even if simple, should be interpreted according to the situation and modified as needed. Of note, if a glucose solution is administered to the patient, it is important to add thiamine to prevent a Wernicke encephalopathy.
- Although multiple pharmacologic options are used to treat SE, there is a substantial lack of comparative, high-level, evidence-based information. Use of a treatment protocol with the three steps is recom-

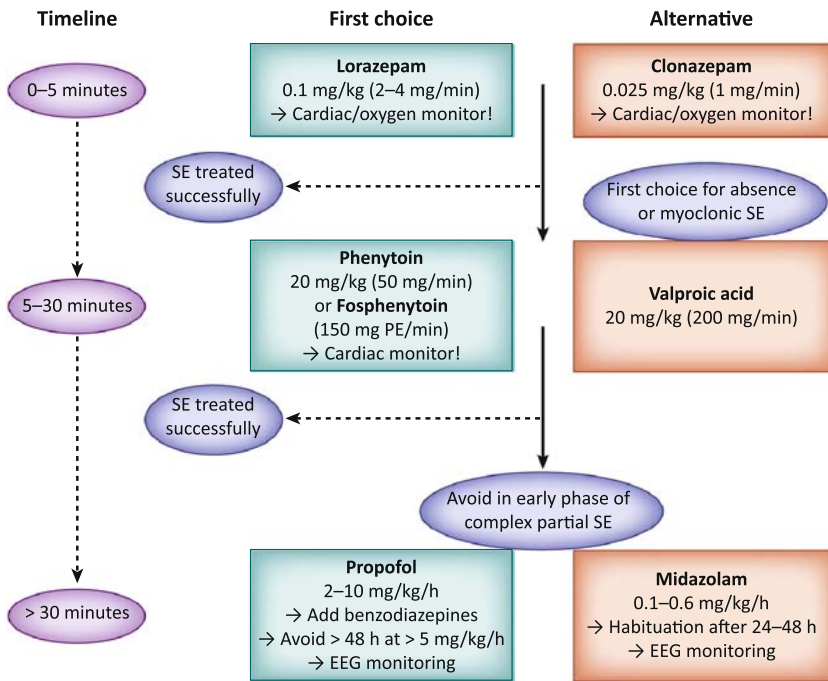


Figure 1. Overview of pharmacologic treatment of status epilepticus (SE). This protocol is by no means highly evidence-based, but only summarizes the author's opinion and experience. EEG—electroencephalography.

mended in order to facilitate and accelerate the early practical management. The patient's background, including etiology and age, largely determines the prognosis, so it is important to consider these aspects and to adapt the treatment strategy to each particular case, in order to minimize the risks of overtreatment or undertreatment. The art of treating SE effectively resides more in the fine-tuning of the approach than in the automatic application of sequential agents. It is hoped that future trials will draw attention to the best strategy for the management of this heterogeneous condition.

First treatment line

- This is the only treatment step that has been studied in several randomized controlled trials. The first, carried out more than 20 years ago on a relatively limited number of patients, disclosed a nonsignificant trend toward better response to 4 mg lorazepam as compared to 10 mg diazepam [6, Class I]. Similarly, a large prehospital trial at the beginning of this decade, using relatively low doses, found that 2 mg lorazepam had a nonsignificant superiority over 5 mg diazepam, both treatments were significantly better than placebo, and cardiovascular and respiratory complications were similar among all three groups [7, Class I], suggesting that SE per se may be responsible for causing hypotension and respiratory depression. A large VA trial, focusing on generalized convulsive SE and assessing the efficacy of 0.1 mg/kg lorazepam, 15 mg/kg phenobarbital, 0.15 mg/kg diazepam followed by 18 mg/kg phenytoin, and 18 mg/kg phenytoin

alone, disclosed better efficacy of lorazepam versus phenytoin alone, but not in comparison to the other arms [8, Class I]. Of note, this was the only trial adapting the dosage to body weight. The overall response in overt SE (about 60%) was higher than in subtle SE (about 20%).

- SE becomes more refractory to treatment with time, and the first treatment has a far better chance of success than the second or third, regardless of the drug (55% vs 7% vs 2% in the VA trial) [9, Class I], so it appears mandatory to administer intravenous drugs that act quickly. In this view, benzodiazepines are the best alternative, over phenobarbital and phenytoin. Compounds with a long elimination half-life in the central nervous system (CNS) are preferred, to minimize the risk of withdrawal or rebound seizures as drug levels decline.
- The administration of a benzodiazepine bolus during SE may induce respiratory and circulatory collapse (about 10% to 26%) [7,8]; therefore, monitoring of these functions is mandatory during administration of benzodiazepines.
- Note that tonic SE in patients with developmental delay, suffering from epileptic encephalopathies, may rarely be aggravated by benzodiazepines.

Lorazepam

Standard dosage	Lorazepam is administered as a slow bolus of 0.1 mg/kg (2 mg/min) it enters the brain in less than 2 to 3 minutes [10] and has a long duration of action (at least 12 h), because it is less likely than diazepam to redistribute in the fat tissue [11]; the protein binding is estimated at 90%. Its elimination half-life is about 8 to 25 h [10,11]
Contraindications	Hypersensitivity to the compound; absence of respiratory monitoring.
Main drug interactions	None.
Main side effects	Sedation, respiratory depression.

Clonazepam

Standard dosage	Clonazepam is administered at a bolus of 0.025 mg/kg. It reaches the brain within 1 minute [10], and, despite its lipophilia, has a stable action over time. It has a plasma half-life of up to 38 h and moderate protein binding (65%) [12]. It is relatively widely used in Europe, but it is not approved by the US Food and Drug Administration as a treatment for SE.
Contraindications	Hypersensitivity to the compound; absence of respiratory monitoring.
Main drug interactions	None.
Main side effects	Sedation, respiratory depression.

Midazolam

Standard dosage	Midazolam usually is given at a dose of 0.1 to 0.2 mg/kg, but doses up to 0.5 mg/kg have been reported [13]. It has a short half-life (about 2 h) but represents a valuable alternative when intravenous lines are not available or in treating children, as intranasal or buccal administration is possible. Protein binding is very high (97%).
Contraindications	Hypersensitivity to the compound; absence of respiratory monitoring.

Main drug interactions	None.
Main side effects	Sedation, respiratory depression.

Diazepam

Standard dosage	Diazepam is administered intravenously at 0.2 mg/kg (5 mg/min); it enters the brain in less than 10 s, but its free fraction redistributes in fat tissue owing to its high lipophilia. Therefore, after about 20 minutes, drug levels in the brain decline significantly [11]. It is tightly bound to proteins (99%). This agent also may be administered rectally—a helpful alternative, especially for children.
Contraindications	Hypersensitivity to the compound; absence of respiratory monitoring.
Main drug interactions	None.
Main side effects	Sedation, respiratory depression.

Second treatment line

- No large-scale, prospective comparative assessments among AEDs used as second-line or third-line SE treatment have been performed to date. The VA study included an arm using phenytoin (which acts principally through sodium channel modulation) as initial SE treatment and an arm using phenobarbital (mainly a GABA_A agonist); it found a nonsignificant trend toward better efficacy with phenobarbital (58% vs 44% [8]).
- Intravenous valproate has been repeatedly reported to be efficacious for several SE types [14,15], probably in view of its multimodal pharmacodynamic action, including GABA, sodium channel, and calcium channel modulations. It lacks significant cardiovascular adverse reactions, so there is no need of concurrent monitoring, a potential advantage in out-of-hospital situations. Some studies comparing it with phenytoin were recently published [14,16,17; Class III], but they are relatively small and suffer from major methodologic pitfalls.
- Levetiracetam has also been employed in SE treatment for several years [18]; the recent availability of an intravenous form renders it even more promising [19,20; Class IV]. It has good tolerability, but no comparative trial has been published to date.
- The recently marketed lacosamide was available in an intravenous form from the beginning; it acts by modulating the slow inactivation of the sodium channel and by interfering with the collapsin protein function. Experience in SE is still anecdotal, however [21, Class IV].
- After loading of one of these agents, serum levels should be checked periodically to ensure therapeutic concentrations.

Phenytoin

Standard dosage	Phenytoin is loaded at 20 mg/kg (maximal infusion rate, 50 mg/min). Maximal concentrations in the CNS are reached after 20 minutes [11]. The elimination half-life is about 24 h, but it becomes significantly longer at high serum levels. A slower infusion rate is especially advisable for elderly patients, and cardiac monitoring should always be performed during intra-
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venous administration. Phenytoin is probably the most frequently used second-line agent.

Contraindications	Complex cardiac arrhythmias, absence of cardiac and respiratory monitoring.
Main drug interactions	Phenytoin is a potent enzyme inducer.
Main side effects	Some rare but serious local reactions (eg, purple glove syndrome) are induced by the alkaline solution, whereas phenytoin itself was associated with hypotension (27%) and bradyarrhythmia (7%) in the VA study group [8].

Fosphenytoin

Standard dosage	Fosphenytoin is a water-soluble phenytoin prodrug that lacks propylene glycol and therefore is safer as regards local tissue reactions. It is dosed in phenytoin equivalents (PE). Although it can be infused at a faster rate than phenytoin (150 mg PE/min), it is questionable whether effective CNS concentrations are reached more quickly than when phenytoin is administered at optimal rates [22].
Contraindications	Same as phenytoin.
Main drug interactions	Same as phenytoin.
Main side effects	Hypotension and bradyarrhythmia.
Special points	Cost limits its availability in some countries.

Phenobarbital

Standard dosage	Phenobarbital is loaded at 15 mg/kg (100 mg/min). It reaches the brain after 20 to 40 minutes and has a long half-life of about 100h.
Contraindications	Absence of cardiac and respiratory monitoring.
Main drug interactions	Phenobarbital is a potent enzyme inducer.
Main side effects	Phenobarbital also bears a consistent risk of hypotension (34% in the VA study [8]).
Special points	The use of phenobarbital as a first-choice second-line agent is relatively rare.

Valproic acid

Standard dosage	Valproic acid is loaded at 20 mg/kg, at high rates (up to 200 mg/min [14,23]) its elimination half-life is about 15 h. Valproic acid enters the CNS rapidly through active transport [24]. Clinical experience in SE suggests that effective CNS concentrations are reached within 30 minutes [23,25]. Its main advantage is the lack of cardiodepressive reactions.
Contraindications	Active hepatitis, pancreatitis, mitochondrial disorder.
Main drug interactions	Valproic acid is an enzyme inhibitor.
Main side effects	At times, follow-up of ammonium counts (especially in patients with persisting slow EEGs) may be advisable, in order to detect an hyperammonemic encephalopathy.
Special points	Valproic acid is increasingly used for SE, especially in settings devoid of cardiac and respiratory monitoring. Moreover, it represents the first choice for absence or myoclonic SE.

Levetiracetam

Standard dosage	Levetiracetam may be loaded up to 20 mg/kg [20•] its plasma half-life is about 7 h, but its bioavailability within the blood-brain barrier is probably
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longer [26]. It is still unclear how quickly levetiracetam reaches the brain. Monitoring of platelet counts may be advisable [19•].

Contraindications	Hypersensitivity to the compound.
Main drug interactions	None.
Main side effects	The most frequent adverse event is mild sedation; no cardiovascular reactions have been reported.
Special points	More expensive than other second-line agents.

Lacosamide

Standard dosage	Loading doses of up to 400 mg have been described [21•].
Contraindications	Hypersensitivity to the compound.
Main drug interactions	None known.
Main side effects	Mild sedation.
Special points	More expensive than other second-line agents; only anecdotal reports to date.

Third treatment line

- In generalized convulsive SE, the first treatment administered is the most likely to be effective [9,27]. For this reason, it seems reasonable to proceed straight to third-line treatment once the second-line (which takes at least 20 to 30 minutes to be effective) has failed [2,28••]. The available studies on refractory SE consist of more or less large case series. A meta-analysis comparing barbiturates with propofol (both acting mainly through modulation of GABA_A receptors) and midazolam did not show any significant difference in short-term mortality with these three agents, although some variations were noted in efficacy (somewhat better for barbiturates) and tolerability (somewhat worse for barbiturates); the patients treated with barbiturates were more likely to be monitored with EEG, however, which may explain some of the differences [29, Class IV]. A retrospective analysis taking into account possible anesthetic combinations did not disclose any notable outcome difference among the agents, whether used alone or in association [30, Class IV].
- There is also considerable uncertainty about the optimal extent of pharmacologic EEG suppression [30] and treatment duration. An EEG target of burst suppression with an interburst interval of about 10 s, maintained for 24 to 36 h and followed by progressive tapering over 12 to 48 h, represents a good, practical option, but this regimen is not yet supported by any comparative assessment.

Barbiturates

	These agents include thiopental in Europe or its metabolite pentobarbital in North America.
Standard dosage	Induction with pentobarbital is performed with boluses of 5 to 15 mg/kg the maintenance dose is 1 to 5 mg/kg per hour. Thiopental is loaded at repetitive boluses of 2 mg/kg and then relayed with a drip of 3 to 5 mg/kg per hour.

These agents show a long half-life after continuous administration (pento-barbital, 15h22h; thiopental, probably slightly longer) [31], and they have a considerable tendency to accumulate in fat tissue, prolonging the need for mechanical ventilation.

Contraindications Need for short-term mechanical ventilation (eg, patients with chronic obstructive pulmonary disease).

Main drug interactions Barbiturates are potent enzyme inducers.

Main side effects Hypotension and respiratory depression.

Propofol

Standard dosage The loading dose is 2 mg/kg, followed by maintenance at 2 to 10 mg/kg per hour. Propofol has a short half-life (about 1–2 h [32]), allowing rapid titration and withdrawal.

Contraindications Metabolic acidosis, hypertriglyceridemia, mitochondrial disorder.

Main drug interactions None.

Main side effects Sedation and respiratory depression. Especially in young children, it may induce the “propofol infusion syndrome” (PRIS), a potentially fatal cardiovascular collapse characterized by lactic acidosis, hypertriglyceridemia, rhabdomyolysis, and green-colored urine; PRIS has been rarely described in patients with SE [33,34•]. Concomitant benzodiazepine administration (eg, a clonazepam or midazolam drip or repetitive short infusions of lorazepam) could lower the propofol dose needed to obtain seizure control, possibly reducing the risk of this complication [35]. Administration of doses over 5 mg/kg per hour for longer than 48 h should be avoided, and repetitive checks of serum lactate could help to detect a beginning PRIS in time to discontinue propofol.

Midazolam

Standard dosage Midazolam is loaded at 0.2 mg/kg, and then maintained at 0.1 to 0.6 mg/kg per hour. It has a half-life of 6 to 40 h after prolonged infusion [36], with an important habituation (tachyphylaxis) developing within 24 to 48 h [37].

Contraindications Hypersensitivity to the compound.

Main drug interactions None.

Main side effects Sedation and respiratory depression.

Special points In view of the tachyphylaxis, which requires large dosage increases after the first day, it may be advisable to switch to one of the other options if prolonged treatment becomes necessary.

Other treatment approaches for persistent, refractory SE

- When SE proves resistant to the first three lines of treatment, usually several days have elapsed since the beginning of the episode. At this moment, it is advisable to attempt switching to another anesthetic of the third line; doing this gives some time to titrate one further second-line compound. It is paramount not to forget to periodically address SE

etiology, because SE prognosis appears to be related mainly to etiology rather than to treatment approach [30,38•,39•]. Some cases of SE prove extremely refractory, however; this condition has been labeled “malignant” and is encountered somewhat more often in young patients with some form of inflammatory disease [40]. Other treatment strategies, used relatively infrequently, have been described in anecdotal case reports or small series; these may be employed in succession. It is unlikely that these strategies will influence the outcome in a decisive way, but some may be interesting in particular settings. Of course, safety should always remain a priority for the prescribing physician.

- Other anesthetics, such as ketamine, which acts as an NMDA antagonist [41•, Class IV], or isoflurane [42, Class IV], an inhalation compound, could be worth a trial. Ketamine may represent an interesting option in view of the pathophysiology of SE; it should be combined with benzodiazepines in order to minimize the risk of neuronal toxicity.
- High-dose oral topiramate, administered through the nasogastric tube, could be beneficial at times [43, Class IV]; this agent may modulate AMPA receptors, in addition to sodium and calcium channels.
- Verapamil, a calcium channel blocker, inhibits the P-glycoprotein, a multidrug transporter diminishing AED availability in the brain. Few case reports on its use in humans with SE are available. It appears relatively safe (under cardiac monitoring) up to dosages of 360 mg/d [44, Class IV].
- The ketogenic diet has been prescribed for decades, mostly for children, to control refractory seizures; its use in refractory SE as a last resort has been described occasionally [45, Class IV]. Its effect is exerted over several days to a few weeks.
- Immunomodulatory approaches such as steroids, intravenous immunoglobulin, or plasma exchanges are often tried in patients with very refractory SE [46, Class IV], at times even without evidence of an underlying inflammatory etiology.
- Potential nonpharmacologic treatments include vagus nerve stimulation initiated in the operating room [47, Class IV], mild transitory hypothermia [48•, Class IV], and resective surgery of an isolated epileptic focus distant from eloquent areas [49, Class IV].

How to “tune” SE treatment

It is my opinion that an important exception to the rule of treating SE quickly and aggressively concerns SE episodes (including absence SE and several forms of complex partial SE) in which patients are at least partly conscious. Indeed, absence SE nearly always resolves without sequelae, and it is still undetermined whether prolonged complex partial seizures in humans induce

permanent structural neurologic damage [50,51]. This differs from generalized convulsive SE, in which damage of limbic structures has been confirmed both pathologically and radiologically. It is thus unclear whether and when coma induction is indicated in forms of SE other than generalized convulsive SE. In fact, this approach could predispose to several complications (eg, pneumonia, deep vein thrombosis, pulmonary embolism, neuropathy, myopathy, ileus) [52].

We recently validated a clinical "Status Epilepticus Severity Score" (STESS) [38•, Class III], allowing an estimation of prognosis before treatment is instituted (Table 1). A favorable score has an excellent negative predictive value (0.97) for mortality: if the score is 0 to 2, the patient will likely survive the SE episode. The score is extremely easy to use and may help to orient early treatment strategy in unclear situations. Patients having a favorable prediction may be managed less aggressively than those who have a potentially dismal prognosis, at least at the beginning. For patients with a favorable score, it appears advisable to try to avoid coma induction by administering nonsedating AEDs. If this approach fails to induce a notable clinical improvement after several hours (up to 24), elective coma induction may then be suggested.

SE episodes in patients with idiopathic generalized epilepsy (absence or myoclonic SE) readily respond to benzodiazepines and valproate; these patients should not be intubated. Conversely, postanoxic SE, the expression of a severe underlying encephalopathy, is often refractory to standard treatments, but in selected cases, after considering other prognostic factors such as brainstem reflexes and somatosensory evoked potentials, antiepileptic compounds (including anesthetics) could be prescribed [53•, Class IV].

In summary, every form of SE should always be treated quickly, but the depth of treatment should be tailored to the clinical situation. It is paramount to continue SE treatment, together with supportive care, in patients with episodes refractory to treatment for several weeks or months, as long as unmistakable evidence of irreversible neurologic damage is not found

Table 1. Status epilepticus severity score (STESS)^a.

Criteria	Features	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple partial, complex partial, absence, myoclonic ^b	0
	Generalized convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 y	0
	≥ 65 y	2
History of previous seizures	Yes	0
	No or unknown	1
Total ^a		0–6

^aA favorable score is 0 to 2

^bComplicating idiopathic generalized epilepsy

[46,54; Class IV]. Once again, one has to keep in mind that etiology, age, and probably comorbidities are the most important predictors of outcome; the exact role of pharmacologic treatment, other than its supportive nature, has not yet been evaluated.

Disclosure

Dr. Rossetti has received speaker fees from UCB, has prepared scientific publications for Janssen-Cilag, and has received research support from Pfizer and UCB.

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