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Antiseizure medications in critical care: an update

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Abstract

Purpose of review—Seizures and status epilepticus are very common diagnoses in the critically ill patient and are associated with significant morbidity and mortality. There is an abundance of research on the utility of antiseizure medications in this setting, but limited randomized-controlled trials to guide the selection of medications in these patients. This review examines the current guidelines and treatment strategies for status epilepticus and provides an update on newer antiseizure medications in the critical care settings.

Recent findings—Time is brain applies to status epilepticus, with delays in treatment corresponding with worsened outcomes. Establishing standardized treatment protocols within a health system, including prehospital treatment, may lead to improved outcomes. Once refractory status epilepticus is established, continuous deep sedation with intravenous anesthetic agents should be effective. In cases, which prove highly refractory, novel approaches should be considered, with recent data suggesting multiple recently approved antiseizure medications, appropriate therapeutic options, as well as novel approaches to upregulate extrasynaptic gaminobutyric acid channels with brexanolone.

Summary—Although there are many new treatments to consider for seizures and status epilepticus in the critically ill patient, the most important predictor of outcome may be rapid diagnosis and treatment. There are multiple new and established medications that can be considered in the treatment of these patients once status epilepticus has become refractory, and a multidrug regimen will often be necessary.

Keywords

anticonvulsants; coma; epilepsy; status epilepticus

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Conflicts of interest

P.M.V. received consultancy fees from Sage Therapeutics within the last 36 months. P.M.V. has an active consultancy relationship with Ceribell, which has produced an FDA-approved rapid-response EEG system. B.A. has no conflicts of interest to report.

INTRODUCTION

The use of antiseizure medications in critical care has undergone a transformation in the last decade with important changes in the use of prophylactic medications and abortive treatment of status epilepticus. In this review, we will provide a brief and focused update on vital new information for intensivists with focused review of recent neurological literature.

Seizures and status epilepticus are two of the most common diagnoses encountered in critically ill patient, accounting for approximately 5–15% of admissions and additionally seen in up to 34% of patients undergoing electroencephalography monitoring in these units. These diagnoses carry a high mortality and morbidity rate. Rapid treatment and cessation of these seizures is important in preventing secondary brain injury in patients with acute brain injuries and in improving patient outcomes. We will focus on recent developments in the treatment of status epilepticus and then focus second on new medications in the prevention and treatment of epilepsy.

UPDATE ON THE TREATMENT OF STATUS EPILEPTICUS

There are several important new lessons in the treatment of status epilepticus for the intensivist to know. First, several recent studies have documented that the treatment of status epilepticus is frequently delayed because of lack of recognition and lack of appropriate first treatment [1[■]]. This delay corresponds to worsened outcome attributable to the delay in treatment rather than the disease process [1[■],2]. The delay can be alleviated by creating a standardized treatment protocol, which features early use of appropriate dose of a seizure abortive medication [3[■]]. Second, the rapid use of intravenous lorazepam or the intramuscular use of midazolam appear to be quite beneficial in the very earliest stages of convulsive status epilepticus [4]. The RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Treatment) study reported that intramuscular midazolam resulted in more rapid seizure control, was easier to administer than intravenous lorazepam and was well tolerated in the under-resuscitated status epilepticus patient. Third, the use of early continuous electroencephalogram (EEG) is an important feature in the treatment of status epilepticus, and is the principal diagnostic method to determine if refractory status epilepticus is ongoing [5]. Fourth, if status epilepticus is refractory, several studies have now shown efficacy of continuous deep sedation using midazolam, pento-barbital, ketamine or propofol in controlling status epilepticus [6[■],7,8,9[■],10–14]. Fifth, novel approaches to treating status epilepticus including the use of compounds to upregulate extrasynaptic γ -aminobutyric acid (GABA) channels have shown early promise, such as brexanolone [15[■]]. Sixth, the use of continuous EEG monitoring to titrate seizure suppression therapy is recommended [5], with accepted EEG targets, such as burst suppression or seizure suppression most commonly used. Seventh, one should anticipate the common side effects of hypotension, immunosuppression, and respiratory suppression when using treatments for refractory status epilepticus. Eighth, therapeutic metabolic therapy in the form of ketogenic diet induced hyper-ketonemia and mild hypoglycemia has emerged as one potential treatment option for refractory status epileptics in both children and adults [16,17]. Finally, the duration of treatment for refractory status epilepticus can be long, commonly requiring many weeks of

intensive care with repeated weaning of abortive therapy. A comprehensive set of guidelines may be found useful by the reader [18].

Many of the medications used to treat and prevent seizures have remained the same for decades. However, newer drugs have been shown to be as effective in preventing seizures, potentially with fewer side effects and drug–drug interactions. The purpose of this review is to provide an update on the medications available in the intensivist’s armamentarium for these purposes. Table 1 summarizes the progression of medical treatments from emergency seizure abortion, treatment of refractory status epilepticus and secondary prevention/control medications. Although usage of the medications summarized is consistent with standard medical practice, the following are not specifically labelled for use by the Food and Drug Administration (FDA) in the treatment of status epilepticus: brivaracetam, clobazam, lacosamide, levetiracetam, ketamine, perampanel, topiramate, valproate sodium. Brexanolone is undergoing review for initial FDA-approval in the treatment of postpartum depression; usage in the treatment of status epilepticus would be off-label.

NOVEL ANTISEIZURE MEDICATIONS

Brivaracetam

Brivaracetam (BRV) is a racetam-type molecule, which works in a similar manner to levetiracetam (LEV) by targeting the synaptic vesicle 2A membrane protein (SV2A). BRV is more selective than LEV with a higher affinity for the target [19]. Although this target is well known, the precise role for SV2A and the downstream consequences of the binding of BRV and LEV to the molecule remains largely unknown [20]. In addition to its higher affinity, BRV is more lipophilic, and has been shown in animal models to penetrate the blood–brain barrier more quickly than LEV [21]. Additionally, BRV exhibits rapid oral absorption, with peak serum concentrations noted 0.5–2 h after administration of the medication [22,23].

In a recent, single-center retrospective study, intravenous BRV was administered over 15 min, and successfully broke status epilepticus in four of seven patients, all of whom were in the early stages of status epilepticus [24]. No adverse cardiopulmonary events were noted in this study, and levels of other anti-epileptic drugs were unchanged after the addition of BRV to the treatment regimen. In a separate multicenter case series, BRV-treatment response was noted in 27% of 11 patients with status epilepticus[25]. Given its rapid distribution, favorable side effect profile, and availability in intravenous and oral formulations, BRV warrants additional study in the neurocritical care setting.

Clobazam

Although clobazam was not approved in the United States until 2011, it has been used since the 1990s in Europe because of similar efficacy and decreased sedation when compared with clonazepam. Although considered part of the benzodiazepine class of medications, clobazam has a slightly different base structure, imparting decreased affinity to the α_1 subunit, and increased affinity to the α_2 subunit of the GABA_A receptor. Animal models suggest that it

may be more effective in GABA-deficient tissues, which suggests it may have increased utility in status epilepticus [26].

Similar to other novel drugs discussed in this review, there have been no randomized controlled studies examining the use of clobazam in status epilepticus. There have been several retrospective studies, case reports, and case series, which have found varying degrees of success in the utilization of clobazam [27[■],28–41]. These reports are limited by sample size, heterogeneity of patients, and heterogeneity in the timing and dosage of clobazam. However, they do suggest that clobazam should be well tolerated to use in in status epilepticus, and could be considered as an add-on in patients with refractory status epilepticus. Prospective data and randomized controlled trials should be utilized to further clarify its utility and optimize usage, timing, and dose.

Lacosamide

Lacosamide was initially approved by the FDA in 2008 as an adjunctive therapy for partial-onset seizures. It utilizes a novel mechanism of action by enhancing slow inactivation of sodium channels and modulation of collapsing response mediator protein 2 [42]. Due to its relatively benign safety profile, minimal interactions with other medications, and availability in intravenous formulations, it has been adopted for use in multiple other scenarios. In the neurocritical care unit, it has been used for seizure prophylaxis after craniotomy, subarachnoid hemorrhage (SAH), and traumatic brain injury, for the treatment of convulsive and nonconvulsive seizures, and as a secondary treatment for status epilepticus [43].

In a recent pilot study, lacosamide was compared with valproate sodium for the treatment of lorazepam-resistant status epilepticus [44]. In this study, it was found to be equally effective and well tolerated when compared with valproate sodium; however, was underpowered to determine noninferiority. In another small randomized study, it was found to be similar in efficacy and safety to fosphenytoin for the treatment of nonconvulsive seizures in critically ill patients [45[■]]. Other retrospective and observational studies have found it to be well tolerated and comparatively effective as an adjunct for seizure prophylaxis after craniotomy, as well as for the treatment of status epilepticus [46–51,52[■], 53,54[■],55[■],56–63]. However, there are no randomized, controlled studies attempting to confirm these findings. There is additionally animal data available to suggest that lacosamide acts as a neuroprotective agent in status epilepticus [64] and traumatic brain injury [65] through its modulation of CRMP, and may decrease epileptogenesis. Given these highly encouraging findings, further study of lacosamide in a randomized, controlled environment would be highly interesting.

Perampanel

Perampanel (PER) is a noncompetitive a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, approved by the FDA in 2012 as an adjunctive treatment for focal onset and primary generalized tonic-clonic seizures. It is primarily metabolized by the CYP3A4 pathway, and as such is decreased in availability by phenytoin and other CYP3A4 inducers [66]. In refractory and super-refractory status epilepticus, there is down-regulation of GABA receptors, which can limit the effectiveness of benzodiazepines and barbiturates. Due to its action on a different receptor, there have been some preliminary

studies on its potential to stop seizures in patients with refractory and super-refractory status epilepticus.

In an animal model of benzodiazepine-resistant status epilepticus, PER was shown to successfully terminate seizure activity [67]. However, the studies in humans with PER in status epilepticus have been significantly limited by sample size, heterogeneity of patients, and significant variability on the timing of PER administration; there have been no randomized-controlled studies on its use. In the few retrospective reviews on its use, utility has been demonstrated, successfully terminating status epilepticus in 17–100% of patients with limited side effects [68,69–77]. Although the data is limited, because of the nature of refractory and super refractory status epilepticus, it is reasonable to consider the use of PER as an add-on in these patients with limited safety concerns.

ESTABLISHED ANTISEIZURE MEDICATIONS

Levetiracetam

Although considered one of the novel agents, levetiracetam was approved for use in the United States nearly 20 years ago and is commonly used because of its favorable side effect profile and limited drug–drug interactions. A major study recently stopped, Established Status Epilepticus Treatment Trial [78], compares the efficacy of levetiracetam, fosphenytoin, and valproic acid for the treatment of benzodiazepine-refractory status epilepticus; results are still pending. Other small randomized, observational, and retrospective studies have shown levetiracetam to be equivalent to phenytoin and valproic acid for these patients [79–83]. However, a recent meta-analysis has found these equivalencies to be because of underpowered studies and throw into question the validity of the conclusions [84].

Levetiracetam is also frequently used as seizure prophylaxis after acute brain injuries and craniotomies. In comparison with phenytoin, it has been shown to be equivalent in the prevention of seizure after severe TBI with improved outcomes at 3 and 6 months with 7 days use after injury in one prospective, randomized, single-blind study [85]; in another smaller prospective cohort analysis, this finding was not confirmed [86]. In examining the utility of levetiracetam in the postoperative setting for intracranial tumor resection, it was found to be effective in preventing acute seizure and likely equivalent to phenytoin [87,88]. Finally, phenytoin and levetiracetam were retrospectively compared in seizure prophylaxis for SAH with equivalent outcomes and likely increased tolerability of levetiracetam because of high cross-over rates [89].

Topiramate

Topiramate is a carbonic anhydrase inhibitor initially approved for the treatment of partial-onset seizures in 1997. It is additionally used for the treatment of migraines, pain disorders, and mood disorders because of its apparent broad therapeutic targets, including voltage-gated sodium channels, high-voltage-activated calcium channels, GABA- α receptors, AMPA receptors, and carbonic anhydrase isoenzymes [90]. Although no randomized controlled trials have been run comparing the effectiveness of topiramate to other antiseizure

medications in the setting of refractory status epilepticus, several retrospective and observation studies, and multiple case reports and case series have shown its utility [91[■],92–99]. Given its limited significant adverse effects, it is reasonable to consider topiramate as an add-on medication in refractory status epilepticus.

SPECIAL CIRCUMSTANCES

Pregnancy

Status epilepticus can occur during pregnancy from a multitude of causes [31], and aside from eclampsia, the optimum treatment regimen is unclear. The incidence is unclear, however, in separate retrospective reviews appears to represent 2–5% of status epilepticus cases [31,100,101]. Given the high mortality rate of status epilepticus in general, prompt control of seizures should be the main goal in all cases, with obvious consideration given to the health of the fetus. Of the medications routinely used for status epilepticus, benzodiazapines, levetiracetam, and phenytoin appear to impart the least risk to the fetus [102], although no randomized controlled studies have been performed to confirm these findings. Although valproate sodium is considered well tolerated for use during the postpartum period [103] in pregnancy-related seizures and status epilepticus, it should be avoided during pregnancy because of a significant risk of major fetal malformations [102,104–107]. Malformations associated with in-utero exposure to valproate sodium include neural tube defects, hypospadias, cardiovascular malformations, and oral clefts.

Antibody-mediated status epilepticus

Antibody-mediated or autoimmune status epilepticus is a more recently described phenomenon, accounting for approximately 2% of status epilepticus cases according to retrospective study [108]. The outcome appears to be highly variable [109], and an optimal treatment regimen has not been described. Treatment should likely focus on treatment of the underlying condition with immunomodulatory therapy to maximize the effectiveness of traditional antiseizure medications [110].

Seizure prophylaxis

Seizure prophylaxis in the neuro-ICU is frequently used after craniotomy, intracerebral hemorrhage (ICH), SAH, and traumatic brain injury. The data supporting this practice is limited overall, however, the risk posed by seizures in these patients is considered high for causing secondary injury.

After severe traumatic brain injury, phenytoin has historically been the medication of choice for seizures prophylaxis [111–114]. More recently, evidence has grown in support of levetiracetam as the first choice because of similar efficacy, decreased adverse effects, and potentially improved late outcomes [83,84[■]]. There is early evidence that lacosamide may also be a well tolerated and effective alternative to phenytoin [57,62,63]. Per the most recent Brain Trauma Foundation guidelines [115], phenytoin remains the recommendation to decrease the incidence of early posttraumatic seizures, but not for the prevention of late posttraumatic seizures or posttraumatic epilepsy. Duration of treatment should be limited, with some data suggesting 7 days of therapy in the absence of seizure detection [112].

In patients with spontaneous ICH, seizure prophylaxis is not recommended per the most recent American Heart Association guidelines [116], because of an association between antiseizure medication use, especially phenytoin, and poor outcomes [117–119]. Since the publication of these guidelines, there has been a significant increase in the utilization of levetiracetam as seizure prophylaxis in these patients [120], with limited evidence showing no worsening of outcomes on follow-up [117]. There is no guideline for the duration of treatment, but given the potential for adverse effects, a limited duration is recommended.

In-hospital seizures are common after SAH, and are associated with poor outcomes [121–124]. On the basis of the most recent American Heart Association guidelines, seizure prophylaxis may be considered in the immediate posthemorrhagic period [125]. Levetiracetam appears to be better tolerated than phenytoin [89], and phenytoin use is associated with functional and cognitive disability in these patients [126]. Given the association between some seizure medication utilization and worse outcomes, it is our practice to limit the duration of treatment in the absence of seizure detection.

Postcraniotomy seizure prophylaxis is routine, but the evidence supporting its use remains limited [127]. Phenytoin, levetiracetam, and lacosamide appear well tolerated [63,88], with phenytoin associated with increased incidences of hypotension [111]. There is no clear guideline for duration of treatment. Given the potential for adverse effects, limiting duration of treatment appears warranted.

In all neurocritical care patients with waxing and waning mental status, persistently depressed mental status, or clinically suspected seizures, EEG monitoring is recommended, regardless of cause. This is our recommendation based on the high prevalence (~20%) of seizures, especially nonconvulsive seizures, in critically ill patients [128]. Duration of monitoring should be up to 3 days in noncomatose patients and up to 7 days in comatose patients in the absence of seizure detection.

CONCLUSION

Although there are many new treatments to consider for seizures and status epilepticus in the critically ill patients, the most important predictor of outcome may be rapid diagnosis and treatment. In addition to antiseizure medications in the traditional sense, a novel medication aimed at increasing the availability of GABA in the extrasynaptic spaces shows promise for the successful weaning of anesthetic therapy. There are multiple new and established medications that can be considered in the treatment of these patients once status epilepticus has become refractory, and it is unclear what order these medications should be added, given a lack of clinical trial data comparing efficacy with sufficient sample size. Barring signs of irreversible injury, outcomes can still be positive with prolonged treatment and multiple attempted weans.

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KEY POINTS

- Delays in diagnosis and treatment of status epilepticus correspond with worsened outcomes.
- Early continuous EEG provides the principal diagnostic method to determine if refractory status epilepticus is ongoing after emergent treatment.
- Multiple novel antiseizure medications in both enteral and parenteral preparations have shown promise in the treatment of refractory and super-refractory status epilepticus.
- Properly designed clinical trials with adequate sample sizes should be performed to better assess these new medications.
- Treatment of status epilepticus can be prolonged, requiring weeks of anesthetics and multiple attempts at weaning.

Table 1.

Summary of progression of medical treatments

Agent	Setting	Main utility	Adverse effects
Emergency use			
Lorazepam intravenous [4,18]	Prehospital, ER, ward, ICU	Rapid onset of action	Respiratory suppression, sedation
Midazolam nasal/i.m./i.v. [4,18]	Prehospital, ER, ward, ICU	Rapid onset of action without need for i.v. access	Respiratory suppression, sedation
Diazepam PR/i.m./i.v. [18]	Prehospital, ER, ward	Rapid onset of action, with availability of needleless routes of administration	Inferior to midazolam in prehospital setting; respiratory suppression, sedation
Phenytoin/fosphenytoin [18,45,78–82]	ER, ward, ICU	Strong evidence regarding efficacy	QT prolongation, cardiac arrhythmia, hypotension
Phenobarbital [18,81]	ER, ward, ICU	Strong evidence regarding efficacy	Respiratory suppression, hypotension
Valproate sodium [18,78,81,82]	ER, ward, ICU	Strong evidence regarding efficacy	Hepatotoxicity, hyperammonemia, pancreatitis, thrombocytopenia
Levetiracetam [18,77–82]	ER, ward, ICU	Fewer significant adverse effects, limited drug-drug interactions	Delirious
Refractory status abortion			
Brexanolone [15]	ICU	Weaning of third-line anesthetics in super-refractory status epilepticus	
Brivaracetam [24,25]	ER, ward, ICU	Limited adverse side effects, limited drug-drug interactions, alternate mechanism of action	Potential metabolic acidosis and cardiovascular collapse with prolonged high-dose infusion
Clobazam [27,28–41]	Ward, ICU	Less sedating than first-line benzodiazepines	P-R interval prolongation
Ketamine [8,9,10]	ER, ICU	Utility in refractory and super-refractory status epilepticus	Delirious
Lacosamide [43,44,46–51,52,53,54,55,56–61]	ER, ward, ICU	Limited adverse side effects, limited drug-drug interactions, alternate mechanism of action	Respiratory suppression, sedation
Levetiracetam [18,77–82]	ER, ward, ICU	Limited adverse side effects, limited drug-drug interactions, alternate mechanism of action	Respiratory suppression, sedation, hypotension
Midazolam [6,11,12,18]	ER, ICU	Mainstay in refractory pediatric status epilepticus	Serious psychiatric and behavioral changes, delirious
Pentobarbital [6,18]	ER, ICU	Mainstay in refractory pediatric status epilepticus	Respiratory suppression, hypotension
Perampanel [66,67,68,69–75]	Ward, ICU	Consideration in super-refractory status epilepticus	Respiratory suppression, hypotension
Phenobarbital [18,81]	ER, ward, ICU	Strong evidence regarding efficacy	QT prolongation, cardiac arrhythmia, hypotension
Phenytoin/fosphenytoin [18,45,78–82]	ER, ward, ICU	Strong evidence regarding efficacy	
Propofol [11–14,18]	ER, ICU		

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Agent	Setting	Main utility	Adverse effects
Topiramate [89,90, 91■,92–97]	Ward, ICU	Potential utility in refractory status epilepticus	Neuropsychiatric symptoms
Valproate sodium [18, 78,81,82]	ER, ward, ICU	Strong evidence regarding efficacy	Hepatotoxicity, hyperammonemia, pancreatitis, thrombocytopenia
Secondary prevention/control			
Lacosamide [45■,52■]	ICU	Similar efficacy to phenytoin in TBI with improved tolerability	
Levetiracetam [83, 84■,85–87]	ICU	Possible fewer long-term cognitive side effects compared with phenytoin	
Phenytoin [83,84■,86,87]	ICU	Brief treatment for TBI	Poor outcomes in SAH, ICH

ER, emergency room; i.m., intramuscular; i.v., intravenous; ICH, intracerebral hemorrhage; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage.