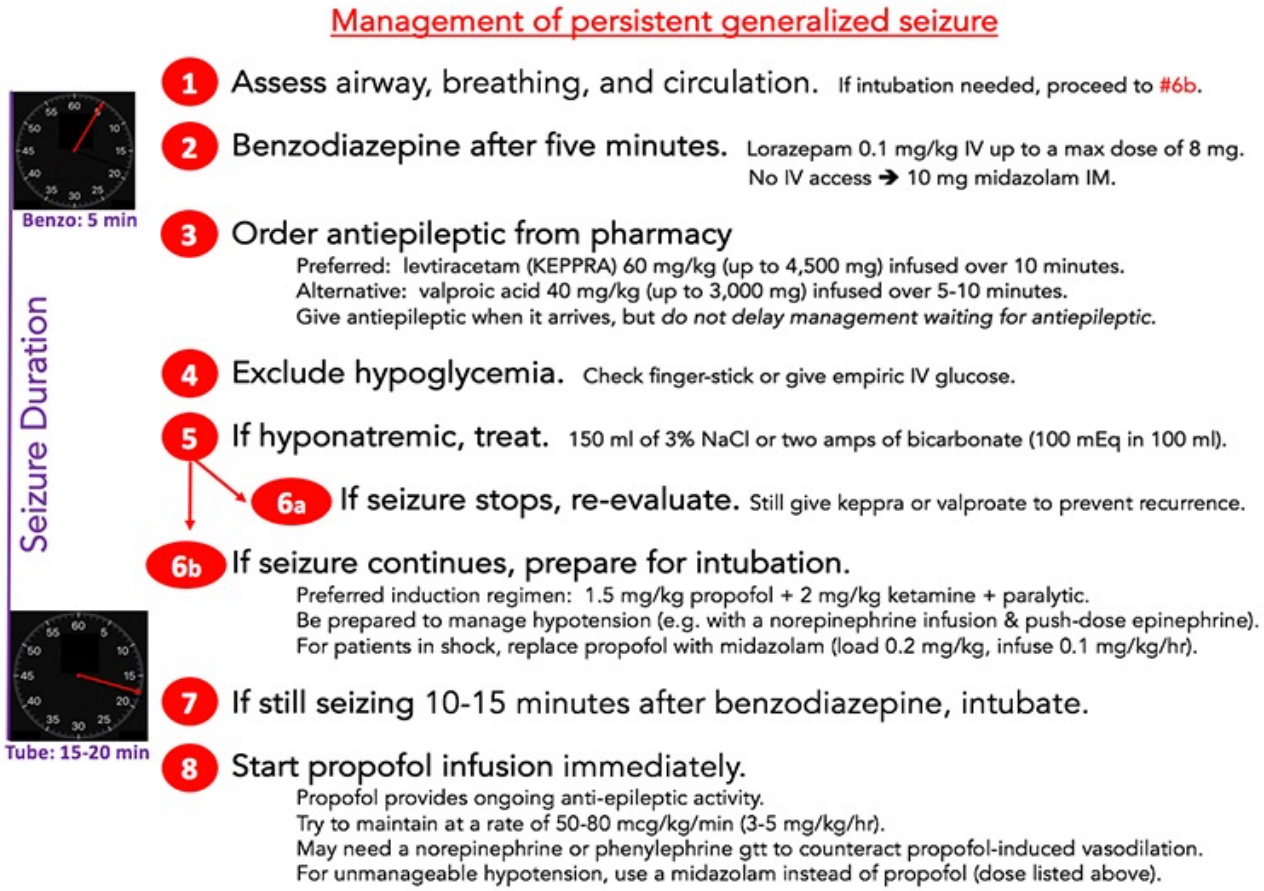
Status Epilepticus Treatment



Benzodiazepine: First-line therapy

For patients with IV access, lorazepam is generally accepted as the first-line therapy. This is based largely on the landmark VA Cooperative Trial, a prospective RCT comparing lorazepam to other antiepileptics including phenobarbital and phenytoin.

The dose of lorazepam used in the VA Cooperative Trial and most is 0.1 mg/kg. This is arguably the most evidence-based dose. However, guidelines usually recommend a dose of 4 mg IV, with a repeat dose if needed.

The algorithm above utilizes 0.1 mg/kg of lorazepam, which may seem like a lot. However, this dose *reduces* the rate of respiratory depression experienced during status epilepticus compared to placebo, indicating that benzodiazepine is *less*

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dangerous than ongoing seizure activity. It should also be noted that pediatric studies and guidelines recommend a dose of 0.1 mg/kg for children.

For patients without intravenous access, evidence supports a dose of 10 mg intramuscular midazolam. The RAMPART study found that up-front intramuscular midazolam was more effective than first attempting to get IV access and then giving IV lorazepam.

Causes of seizure that require immediate treatment

There are dozens of causes of status epilepticus. However, for immediate management two are the most important: hypoglycemia and hyponatremia.

Hypoglycemia must be excluded in any patient with seizure or altered mental status. This can generally be accomplished by measuring a fingerstick glucose. If fingerstick glucose can't be obtained or is borderline, just give IV dextrose (e.g., 1-2 ampules of D50W).

Hyponatremia may also require immediate treatment. If electrolytes aren't known, they should be measured (ideally with a point-of-care device which will provide rapid results). Hyponatremia can be treated by bolusing ~150 ml of 3% saline, with a repeat bolus for persistent seizures. However, this often takes a while to obtain from pharmacy. Two ampules of hypertonic bicarbonate provide a similar amount of hypertonic therapy, with the advantage that they are immediately available.

Intubation using propofol

Propofol as a second-line antiepileptic agent

The rationale for propofol as a second-line anti-epileptic (rather than waiting for a conventional anti-epileptic agent) has been well researched; in short, most patients who fail benzodiazepine will require intubation eventually. Delaying intubation to allow for a trial of anti-epileptic risks prolonging the seizure and increasing associated complications.

Propofol is a potent anti-epileptic agent. When bolused during rapid sequence intubation, this will usually break the seizure. Propofol must subsequently be infused at a moderate dose (e.g., 50-80 mcg/kg/min) to *maintain* control of the seizure.

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The advantage of propofol is that it is rapidly *titratable*. Thus, a high dose of propofol may be used initially to gain control of the seizure. Once the seizure is controlled and the dust has settled, propofol may be down-titrated as needed.

The main disadvantage of propofol is that it causes hypotension. This is generally manageable (e.g., with a low-dose norepinephrine or phenylephrine infusion). However, for a patient with severe shock, propofol may not be safe. These patients may be managed using midazolam instead (with a loading dose of 0.2 mg/kg, followed by an infusion of 0.1 mg/kg/hr).

Prolonged infusion of propofol at high rates can cause propofol infusion syndrome (a highly morbid condition involving bradycardia, lactic acidosis, and shock). This may be avoided by using propofol infusion rates below 83 mcg/kg/min (<5 mg/kg/hr) and serial monitoring of triglyceride levels.

Ketamine as an adjunctive antiepileptic agent

Ketamine is a powerful anti-epileptic agent. For example, ketamine has shown efficacy in status epilepticus refractory to a variety of other medications. Consequently, some guidelines have added ketamine as a possible treatment for super-refractory status epilepticus.

The combination of ketamine and propofol should theoretically provide *synergistic* anti-epileptic activity. Propofol stimulates the GABA receptors (the main inhibitory neurotransmitter in the brain), whereas ketamine inhibits NMDA receptors (a major excitatory neurotransmitter). The combination of these two effects causes a profound decrease in CNS activity. Ketamine combined with propofol ("ketofol") was effective in published series of patients with super-refractory status epilepticus.

Choice of paralytic for intubation

The ideal paralytic for status epilepticus is controversial. Rocuronium is an excellent paralytic for intubation, but it will obscure the neurologic examination for about an hour. Prolonged paralysis could create a situation where the patient is having persistent electrical seizures (causing brain damage), without observable movements. There are numerous reasonable approaches to this, including:

- Intubation with succinylcholine (if there is no contraindication to this). Caution is required, however, because ongoing status epilepticus may cause hyperkalemia after >20-30 minutes.

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- Intubation with rocuronium, followed by *reversal* of rocuronium with sugammadex to obtain a neurologic examination.
- If you don't have sugammadex, intubation with rocuronium may still be used. Following intubation, consider giving high dose propofol infusion, additional ketamine, and a conventional anti-epileptic agent to provide extra protection against recurrent seizure while the patient is paralyzed.
- Intubation without a paralytic (a bolus of 1.5-2 mg/kg propofol will generally produce good intubating conditions, albeit for a short time).

Conventional anti-epileptic drug

Equipoise

According to the most recent guidelines, first-line conventional antiepileptic drugs include fosphenytoin, valproic acid, or levetiracetam. Among these, there is no clear evidence regarding which is the most effective.

Fosphenytoin has traditionally been regarded as the first-line antiepileptic agent. This isn't because of evidence of superiority, but rather because there is the greatest amount of prior experience with its use (status quo bias). Given problems with fosphenytoin outlined below, many institutions are moving away from it.

- Fosphenytoin has more adverse drug effects than other agents, especially hypotension and bradycardia (and can lead to cardiac arrest).
- Fosphenytoin has sodium-channel blocking effects, which could be problematic in the setting of status epilepticus due to sodium-channel blocker intoxication (e.g., tricyclic antidepressant). However, it is often impossible to know immediately if a patient's seizure has a toxicological etiology.
- Fosphenytoin has numerous drug-drug interactions, necessitating ongoing measurement of drug levels and perpetual dose titration. Spending five minutes on rounds deciding on the phenytoin dose is a distraction from more important issues.
- Even patients who respond well to phenytoin will usually get transitioned to levetiracetam eventually. Instead of exposing the patient to two different drugs, why not start with levetiracetam in the first place?
- After infusion fosphenytoin must be converted by the body into active drug (phenytoin) before it can work. This is a pharmacokinetic drawback compared to valproic acid and levetiracetam, which likely achieve therapeutic levels in the brain faster.

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Levetiracetam vs. valproic acid?

Both levetiracetam and valproic acid are excellent options. Levetiracetam is often favored because:

- Levetiracetam has nearly no contraindications, which makes it a good choice when giving a medication emergently to someone you know little about. In contrast, valproic acid is contraindicated in some situations (hepatic disease, urea cycle disorders, mitochondrial diseases).
- Levetiracetam is easy to administer (doesn't require monitoring of drug levels).

Timing of conventional anti-epileptic drug

Even if the seizure is controlled with lorazepam, the patient should *still* receive a conventional anti-epileptic drug. Lorazepam will only provide protection against seizures for a few hours. Failing to provide ongoing anti-epileptic therapy leaves the patient at risk for recurrent seizures.

Therefore, any patient who has been seizing for >5 minutes should receive a conventional anti-epileptic drug. There is no merit to delaying this. Ideally, the conventional anti-epileptic agent would be given at the 5-minute mark (simultaneously with the lorazepam).

In reality, ordering the anti-epileptic drug from pharmacy, receiving it, and infusing it will often take ~20-40 minutes. Using the above algorithm, the levetiracetam will usually arrive from pharmacy after the seizure has already been controlled with propofol. Thus, in practice the role of the levetiracetam is generally to prevent recurrent seizure.

Wrapping it up

Following seizure control, additional investigation may be required to determine the cause of the seizure (e.g., CT scan, MRI, LP, toxicology labs, anti-epileptic drug levels, etc.). Any causes and contributory factors should be treated.

Video EEG is helpful to monitor therapy. It is unknown whether it is sufficient to simply control seizures, or whether deeper levels of anesthesia might be preferable (e.g., inducing a burst-suppression or completely flat EEG pattern). The optimal duration of anesthesia is also unknown. A reasonable approach may be to start by

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suppressing seizure activity for a day, and then trying to wean off sedation. With this strategy, most patients will only require a day of mechanical ventilation. Use of high dose maintenance antiepileptics (e.g., levetiracetam) throughout this period may avoid recurrent seizures.