Toxin-related seizures are secondary to an imbalance in the brain’s equilibrium of excitation-inhibition. This delicate balance is maintained via excitatory neurotransmission (e.g., glutamate or the N-methyl-D-aspartate [NMDA] receptor) and inhibitory neurotransmission (e.g., γ-aminobutyric acid [GABA] or the GABA receptor complex). Balance is also dependent on normal ion flux and homeostasis of biogenic amines and acetylcholine. Perturbation of this equilibrium can be the result of the presence of a toxin or the abrupt removal of one (withdrawal). This article reviews the epidemiology, pathophysiology, toxicology, clinical features, and management of toxin-related seizures. Particular emphasis is placed on contrasting the management of toxin-related seizures with seizures of other etiologies, because clinicians are likely to have greater experience, knowledge, and comfort dealing with the latter. Despite the differences, the basic management principles for any seizure are the same: rapidly stabilize the patient and provide supportive care; expediently terminate seizure activity; diagnose the cause of the seizure; and abate associated morbidity and mortality.

EPIDEMIOLOGY

The true incidence of toxin-related seizure is unknown. Prospective study of patients presenting with their first convulsive seizure has found the following: 8.5% of patients older than 25 years have a toxic/metabolic etiology; 11% of patients older than 60 years have a toxic/metabolic etiology; and 24% of patients between 40 and 65 years of age have a toxic/metabolic/vascular etiology. Because there is no discrete reporting of toxin-induced seizures, these data only give parameters within
which the incidence of toxin-related seizures might lie. Retrospective study of first seizure in patients older than 16 years has found 6% of new-onset seizures to be toxin related. In a prospective study of human immunodeficiency virus–positive adults with first seizure, 47% were toxin related.

Box 1 presents a list of the more common agents associated with seizures. Certain toxins impart an elevated risk for seizure: 19% to 87% of isoniazid ingestions; 15% to 37% of buproprion ingestions, and 14% of venlafaxine ingestions. Clinicians should also be cognizant of iatrogenic causes of toxin-related seizures related to the use of local anesthetic agents and flumazenil.

**PATHOPHYSIOLOGY**

There are 4 mechanisms that are associated with toxin-induced seizures:

1. Activity at NMDA and GABA receptors, including GABA synthesis with resultant imbalance in excitation and inhibition
2. Disturbances of ion flux, usually involving sodium channels (either blockade or openers); this alters the resting potential of neural cells (either depolarization or hyperpolarization)
3. Adenosine antagonism
4. Alterations in concentration or activity of biogenic amines and acetylcholine. This mechanism is typified by the fact that seizures may result from either cholinergic excess or an anticholinergic state.

Though seemingly abstract, an understanding of the underlying mechanism can play a significant role in treatment. Despite the numerous mechanisms described, most toxins induce seizures via activity at the GABA receptor complex.

**Glutamate/NMDA and GABA**

Excitatory neural tone that leads to seizure is mediated predominantly by glutamate, aspartate, and similar excitatory neurotransmitters binding at NMDA receptors. The counterbalancing inhibitory tone is mediated predominantly by GABA as well as endogenous benzodiazepine-like neurotransmitters at GABA receptors. Excessive excitatory amino acid (EAA) tone is associated with seizure, while increasing GABA activity results in sedation and ultimately coma. Consciousness is maintained by balancing excitation and inhibition.

Toxin-related seizures as a result of imbalance of EAA and GABA are usually the result of inhibition of GABA tone, which is effectively excitation. EAA concentrations may be increased directly by toxins such as cocaine, or indirectly by toxins that induce ischemia, hypoxia, or hypoglycemia. In either instance, the net effect may result in seizure activity. Toxins that disrupt metabolism, such as hypoglycemic agents, cyanide, and carbon monoxide, result in elevated EAA levels and may cause seizure.

Drugs effecting glutamate/NMDA antagonism typically have potent anticonvulsant and neuroprotective effects whereas those effecting glutamate/NMDA agonism have proconvulsant effects. Nearly all pharmaceutical agents with pure NMDA agonism or antagonism effects are experimental drugs. Imperfect examples of such agents include the anticonvulsant lamotrigine, which diminishes excessive EAA activity, and toxins such as cocaine or soman, which work in part by increasing excitatory amino acids.
Box 1
Partial list of seizure-inducing toxins

Anticholinergics
  Diphenhydramine\(^a\)
Anticonvulsants
  Carbamazepine\(^a\)
  Phenytoin
Cholinergic agents
  Organophosphates
  Nerve agents
Hydrazines
  Isoniazid
Hydrocarbons
  Camphor
  Lindane
Hypoglycemic agents
  Insulin
  Sulfonylureas
Methylxanthines
  Theophylline\(^a\)
  Caffeine
Miscellaneous
  Buproprion
  Citalopram
  Lithium
  Venlafaxine\(^a\)
Mitochondrial Toxins
  Carbon monoxide
  Cyanide
Opioids
  Meperidine
  Propoxyphene\(^a\)
Sodium Channel Blockers
  Lidocaine\(^a\)
  Cyclic antidepressants\(^a\)
Sympathomimetics
  Amphetamines
  Cocaine
Withdrawal
  Ethanol
  Sedative-hypnotic

\(^a\) Toxins also associated with cardiotoxicity and dysrhythmias.
GABA agonists, for example, benzodiazepines or barbiturates, have anticonvulsant effects, whereas GABA antagonists such as flumazenil, lindane, or pentylenetetrazole (Metrazol) have proconvulsant effects.

**Inadequate GABA Production**

GABA is synthesized from glutamate via a pathway that uses glutamic acid decarboxylase (GAD). GAD requires pyridoxal 5'-phosphate as a cofactor (the active form of pyridoxine). Hydrazines such as isoniazid or Gyrometra sp mushrooms disrupt normal production of GABA by numerous mechanisms including blocking pyridoxal 5'-phosphate and enhancing the elimination of pyridoxine. The ultimate toxic effect of hydrazines is an inadequate quantity of GABA, which may result in seizures. In this unique circumstance, use of benzodiazepine or barbiturate anticonvulsants may be ineffective because both require GABA to exert their clinical effect, and in this setting central nervous system GABA concentrations are inadequate. Pyridoxine (vitamin B6) is critical in the management of seizures related to hydrazine poisoning, and is purported to be beneficial in theophylline toxicity, which may depress pyridoxine levels through an unknown mechanism of action.

**Disruption of Normal Ionic Flux**

Brain neurons are continuously dependent on appropriate ion flux to maintain a given state of polarization, depolarization, or repolarization. Seizures may result from an imbalance, and shifting of a given neurologic state out of homeostasis. Whether by increasing sodium channel blockade or sodium channel opening, or increasing either anticholinergic or cholinergic tone, deviation from homeostasis in either direction can result in seizure. **Box 2** provides examples of toxins that affect ion flux and are associated with seizures.

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**Box 2**

Toxins that induce seizure via ion flux and their related mechanisms

- **Sodium Channel Blockers**
  - Camphor
  - Lidocaine
  - Phenytoin
  - Quinidine
- **Sodium Channel Openers**
  - Ciguatoxin
  - Pyrethroids
- **Potassium Channel Blockers**
  - 4-Aminopyridine
- **Potassium Channel Openers**
  - Barium
  - Apamin (bee venom)
  - β-Adrenergic antagonists
  - Propranolol
Adenosine Activity in Seizures

Adenosine is the endogenous neurotransmitter that is responsible for interictal periods. When a seizure does not self-terminate, both EAA levels and GABA levels increase and adenosine release occurs in a burst fashion, resulting in brief electrical silence followed by a resumption of nonictal brainwave activity (Fig. 1). Any interference with this process may result in seizures without interictal periods, clinically evident as status epilepticus. Methylxanthines, such as caffeine and theophylline, are structural analogues of adenosine that do not possess any activity at the adenosine receptor and therefore act as adenosine antagonists. Accordingly, theophylline toxicity is often marked by refractory seizures (see Fig. 1). Caffeine and theophylline have been used to induce more robust and prolonged seizure activity in patients undergoing electroconvulsive therapy. A familiar analogy to this activity is therapeutic use of adenosine to treat tachydysrhythmias. Administration typically results in brief electrical silence (asystole) followed by resumption of normal electrical activity. Adenosine has been reported to have significant efficacy as an anticonvulsant in toxin-related seizures, though further research is needed before it can be recommended as a therapeutic modality.

The dangers of toxic doses of adenosine antagonists in the setting of toxin-related seizures are well known: Status epilepticus associated with theophylline has as high as a 23% incidence of death and a 50% incidence of death or permanent neurologic disability. Seizure activity in a patient with theophylline or caffeine poisoning that is unresponsive to benzodiazepine therapy is also unlikely to respond to phenytoin administration, but may respond well to barbiturate therapy.

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**Fig. 1.** Electrocorticographic ictal-interictal cycling of feline subjects with penicillin-induced seizures. (A) Control. (B) Prolonged interictal phase after dipyridamole (adenosine reuptake inhibitor). (C) Status epilepticus after theophylline administration. (Reproduced from Eldridge FL, Paydarfar D, Scott SC, et al. Role of endogenous adenosine in recurrent generalized seizures. Exp Neurol 1989;103(2):179–85; with permission.)
There are numerous toxins capable of causing seizure that do not fit neatly into the aforementioned categories. Other toxins, such as cocaine, which both increases glutamate release but also acts as a sodium channel blocker, may have multiple mechanisms that induce seizures. Fortunately, the fundamental treatment strategy for toxin-related seizures can be broadly applied, as it is independent of the mechanism by which the seizure was induced.

**COMPLICATIONS ASSOCIATED WITH TOXIN-RELATED SEIZURES**

Complications associated with toxin-related seizures carry significant risks of morbidity and sometimes mortality. Although most toxin-related seizures are not fatal, if status epilepticus is induced the chance of mortality is increased. Toxin-related seizures can result in serious cardiovascular effects. Seizure in an otherwise toxic but stable patient may precipitate dysrhythmias or cardiac arrest, particularly for drugs that affect cardiac conduction or rhythm (see Box 1).11,48–56

Aberrant cardiac conduction, specifically prolonged QRS duration, predicts the likelihood of seizure and occurs with seizure in patients with cyclic antidepressant overdose.57 This phenomenon of cardiac conduction abnormality associated with seizure appears to occur with other seizure-inducing toxins that also affect cardiac conduction, but not with seizures resulting from epilepsy.58 However, seizure with other agents, such as antidysrhythmics, may occur in the absence of an electrocardiograph (ECG) abnormality.59

**INVESTIGATIONS**

Bedside assessment of serum glucose and 12-lead ECG should be used routinely in the evaluation of patients with undifferentiated seizures. Other investigations are discussed here, but are not routinely indicated for toxin-related seizures.

**Computed Tomography**

Computed tomography (CT) should be selectively used for patients with toxin-related seizures. One study did not find any benefit to routine brain CT performed on all patients presenting with altered mental status associated with poisoning or drug overdose.60 However, in a large study of patients presenting with a first alcohol-related seizure, 6.2% of patients had intracranial lesions discovered by CT.61 These varying data are the result of the spectrum of problems that result in toxin-related seizures.

In patients with poisoning that reasonably would be presumed to cause seizure but who have no focal neurologic deficit, a head CT scan is not necessary in the emergency department. This situation requires determination that the seizure is expected to result from the toxin or withdrawal and correlation of the patient’s clinical presentation, to determine that the toxin exposure or withdrawal in question is a likely cause of the seizure in question.

**Drug of Abuse Screening**

Of the drugs of abuse commonly screened for, namely amphetamines, cannabinoids (marijuana), cocaine, opioids, and phencyclidine (PCP), only cocaine is a regular and reliable cause of seizure. In the absence of overt cocaine toxicity, seizure associated with cocaine exposure should not be attributed to this drug. Synthetic opioids (eg, meperidine and propoxyphene) associated with seizure are not detected by routine opioid screening assays. Amphetamines other than 3,4-methylenedioxymethamphetamine (MDMA; “Ecstasy”) as well as PCP infrequently cause seizures. PCP and
amphetamines other than MDMA are only anecdotally associated with seizure and actually have anticonvulsant properties at most sublethal doses. Other than cocaine, it is highly unlikely that a drug of abuse responsible for a seizure would be detected with routine drug of abuse screening. Cocaine-induced seizures occur in only a minority of cocaine users and therefore should be evaluated in the same manner as any first seizure. As such, in the opinion of the authors, drug of abuse screening with the intent of using the results to diagnose or medically manage patients with toxin-related seizures has no clinical value and is not recommended.

**Electroencephalograph Monitoring**

Electroencephalograph (EEG) monitoring is indicated for all patients who have been paralyzed, for the purpose of supportive care during seizure activity. Neuromuscular blockade can facilitate endotracheal intubation for control of airway, and subsequent oxygenation and ventilation and temperature regulation is improved when heat-generating motor activity ceases. However, despite the absence of motor activity, status epilepticus in the paralyzed patient imparts a significant risk of permanent neurologic injury or even death. Whenever possible, EEG monitoring should be performed in the paralyzed patient to ensure appropriate anticonvulsive therapy. The pupillary light response has been demonstrated to be preserved during neuromuscular blockade and barbiturate coma, and may be used as a surrogate when continuous EEG monitoring is unavailable. During generalized seizure activity, pupils are typically dilated secondary to the associated catecholamine surge, effectively extinguishing pupillary response to light. Nonetheless, clinicians should be hesitant to initiate prolonged paralysis in the patient with status epilepticus if EEG monitoring is not available.

Several toxins, such as strychnine, tetanus toxin, and γ-hydroxybutyrate, as well as circumstances such as serotonin syndrome, may result in myoclonus, tremor, tetany, or other motor activity that may be difficult to distinguish from seizure activity. If there is any question about the presence of seizure activity, an EEG is indicated.

**MANAGEMENT OF TOXIN-RELATED SEIZURES**

Supportive care is the most important aspect of toxin-related seizure management. Airway management with appropriate oxygenation and ventilation in conjunction with blood pressure, heart rate, and core temperature stabilization are critical areas of support. In addition, attention must be paid to maintaining appropriate serum glucose and pH. Unfortunately, despite optimal supportive care, permanent neurologic sequela is possible from uncontrolled seizure activity.

Although seizure activity is often self-limited, at times specific anticonvulsant therapies are necessary. Therapeutic regimens designed for epileptic seizures applied to toxin-related seizures can be effective or potentially harmful. As such, the authors recommend an algorithm for managing toxin-related seizures, which is safe if applied to epileptic seizures as well (Fig. 2). Terminating toxin-related seizures is not effected by a simple strategy to restore “balance.” For example, sodium channel blockade–induced seizure is not treated with sodium channel openers: Treatment does not consist of treating with the “equal and opposite” therapeutic agent, but rather by effecting neural sedation by means of supportive care and, in most cases, administration of medications to increase GABA tone.

Initial management of any seizure is identical regardless of the seizure etiology. After airway and cardiopulmonary issues have been addressed and an assessment of
serum glucose has been made, administration of a benzodiazepine is indicated. If, within several minutes, the seizure activity does not terminate, an additional dose of benzodiazepine should be administered. Although the seizure termination efficacy of diazepam, lorazepam, and midazolam appear to be similar, lorazepam has benefits with regard to longer duration of activity, and midazolam is the best choice for intra-muscular administration.

Benzodiazepines

Benzodiazepines remain the mainstay of seizure therapy. While there is often discussion related to which benzodiazepine should be given first, there should be no delay in administering any benzodiazepine to the patient in status epilepticus. Lorazepam is the preferred initial benzodiazepine and can be given to adults at 2 mg/min up to 4 mg and repeated once at 10 minutes if needed. Pediatric (1 month to 12 years) dosing is: 0.05–0.1 mg/kg (maximum: 4 mg/dose) slow IV over 2–5 minutes (maximum rate: 2 mg/minute); may repeat every 10–15 minutes if needed. Diazepam dosing is 5–10 mg IV in adults repeated every 10 minutes as needed to a maximum of 30 mg. Pediatric (1 month to 5 years) dosing is 0.2–0.5 mg/kg IV to a maximum dose of 5 mg, children over 5 years old can receive 1 mg every 2-5 minutes as needed to a maximum of 10 mg. Midazolam has been shown to be effective even when administered via non-intravenous routes. The adult IV dosing for midazolam in status epilepticus is 1–2.5 mg in 2 minute intervals to a maximum of 10 mg. Pediatric dosing is 0.05–0.1 mg/kg to a maximum of dose of 6 mg. Midazolam should be given slowly as it can cause cardiac arrest and has an FDA black box warning to this effect. Also

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**Fig. 2.** Toxin-related seizure management algorithm. It is necessary to continuously reevaluate and correct airway, breathing, circulation, serum glucose, electrolyte, temperature and vital signs abnormalities as appropriate. If diagnosis of specific poisoning is made or suspected, a specific antidote, such as the cyanide antidote kit, phystostigmine, atropine, or pralidoxime, may be indicated. Rapid-acting barbiturates such as pentobarbital or thiopental preferred, phenobarbital is acceptable. Rapid-acting barbiturates are expected to work within 3 to 5 minutes; the therapeutic effect of phenobarbital may take 15 minutes or longer.
of note, high dose midazolam has been shown to terminate seizure activity refractory to other agents and may be considered as a life-saving measure.

**Pyridoxine (Vitamin B6)**

If 2 doses of a benzodiazepine do not terminate the seizure activity, a therapeutic dose of pyridoxine should be given serious consideration. Empiric pyridoxine dosing is 5 g intravenously (IV) in an adult and 70 mg/kg IV in a child. This dose may be adjusted, and pyridoxine can be administered on a gram-per-gram basis with isoniazid in cases of known isoniazid ingestion. Pyridoxine administration is specifically intended to ensure that the patient will have adequate quantities of GABA. This situation is critical in hydrazine poisoning and may be effective in other types of poisoning (eg, theophylline). The effect of this therapy should be apparent within minutes of administration. Unfortunately, the infrequent use of this product and the large quantity needed in the management of toxin-related seizures make it unlikely that it will be readily available for administration. Therefore, if seizure activity has not stopped after 10 minutes from onset, it is appropriate to administer a parenteral barbiturate while awaiting pyridoxine. Phenytoin has not been shown to be effective in this setting.71,72

**Propofol**

This unique agent has activity both at the GABA receptor complex and at NMDA receptors. Propofol induces sedation by increasing GABA tone and antagonizing excitatory tone at NMDA receptor.73 This dual mechanism has a theoretical benefit when treating toxin-related seizures secondary to increased NMDA activity, such as sedative hypnotic withdrawal. Because propofol suppresses neural transmission in a mechanism totally independent of GABA, it can also be instrumental in the treatment of status epilepticus caused by toxins with potent GABA inhibition, such as flumazenil, lindane, and certain pesticides, as well as other toxins, which understandably may not respond to benzodiazepines and barbiturates. Propofol has an extremely quick onset and its effects terminate rapidly. Caution should be used when administering propofol, because it frequently causes respiratory depression. Propofol dosage required for status epilepticus is generally greater than sedation dosing and approaches induction dosing: adults, 2mg/kg-5mg/kg bolus dosing titrating to response. Patients will require endotracheal intubation and ventilation.74,75

**Barbiturates**

The barbiturate with which most clinicians are familiar is phenobarbital. Other barbiturates, such as pentobarbital,76 have several advantages and should also be considered, particularly in cases of status epilepticus.77 Pentobarbital dosing is 5–15 mg/kg loading dose over 15 minutes followed by maintenance infusion of 0.5–3 mg/kg/hour. The clear advantages of pentobarbital, thiopental, secobarbital, or other fast-acting barbiturates include greater potency, high lipid solubility, and more rapid onset of peak activity relative to phenobarbital. In addition, pentobarbital’s activity at the GABA receptor is less dependent on the presence of adequate normal quantities of GABA, a theoretical benefit in treating seizures induced by toxins that deplete GABA.78 These fast-acting barbiturates impart a greater risk of respiratory depression and hypotension relative to phenobarbital. Caution is clearly indicated when using any barbiturate after previous treatment with a benzodiazepine. These drugs work synergistically,79 with benzodiazepines increasing the frequency of GABA chloride channel opening and barbiturates increasing the duration of GABA chloride channel opening.80 Together, they may cause sedation to the point of respiratory depression or
respiratory arrest. If administration of a barbiturate does not successfully terminate the seizure activity, use of propofol at a bolus dose of 1 to 2 mg/kg IV, or an additional dose of barbiturate, should be considered.

**Anticonvulsant Infusion and General Anesthesia**

If bolus dose administration of barbiturates and propofol is unsuccessful, continuous infusion of an anticonvulsant is recommended. Pentobarbital, midazolam, and diazepam have commonly been used for this purpose. Propylene glycol, used as a diluent for certain parenteral benzodiazepine preparations, is a toxic alcohol that may induce toxicity if given as an infusion. Like other toxic alcohols, such toxicity results in an acidemia.81,82 Some reports show a benefit to propofol infusion for the treatment of status epilepticus, though further studies are needed.83,84 Propofol infusion has been anecdotally described as causing a metabolic acidosis, sometimes fatal, by an unknown mechanism.85 These rare adverse drug events are not a contraindication to use these agents, but do warrant regular laboratory assessment to detect the development of acidosis in patients on such infusions.

General anesthesia with inhaled volatile anesthetics, specifically isoflurane, is considered by some as the last line of therapy for refractory status epilepticus, although there are very few data to support their use.86,87

**Miscellaneous Anticonvulsants: Phenytoin, Lidocaine, and Chloral Hydrate**

Phenytoin has been demonstrated to be ineffective for the treatment of isoniazid-induced seizures and withdrawal seizures. Phenytoin can potentially be harmful when used to treat seizures induced by theophylline or cyclic antidepressants.46,47,88–90 Alternative anticonvulsants (mentioned earlier) should be considered prior to the administration of phenytoin in patients with undifferentiated toxin-related seizures.

Lidocaine and chloral hydrate have been advocated as third-line therapy for refractory status epilepticus. Lidocaine is a sodium channel blocker similar to phenytoin, and has been demonstrated to increase morbidity and mortality with certain toxins.91 Chloral hydrate is not available in a parenteral form and is associated with cardiotoxicity.92 As such, neither of these agents is recommended as therapy for toxin-related seizures.

**SUMMARY**

Toxin-related seizures are common and have significant associated morbidity and mortality. The appropriate management of toxin-related seizures differs from the management of epileptic seizures in several ways that are presented in Fig. 2. The management strategy for toxin-related seizures discussed herein can be safely applied to seizures of unknown etiology or epileptic seizures, but the converse is not true.

**KEY CONCEPTS**

- The majority of toxin-related seizures respond to benzodiazepine therapy.
- Pyridoxine should be considered in the treatment of status epilepticus of undetermined etiology.
- Phenytoin should not be routinely administered to patients with toxin-related seizures.
- In all patients with seizures, bedside serum glucose determination is critical.
- Drug screens are rarely helpful in the acute management of patients with seizures.
REFERENCES