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Drug- and Toxin-Induced Seizures

Introduction

Seizures are a common presentation to emergency departments (ED), accounting for approximately 1% of ED visits.[1,2] An estimated 2-5% of the population will experience at least one non-febrile seizure during their lifetime.[3] Seizures can cause serious complications including hyperthermia, acidosis, anoxic brain injury, an eight-fold increased risk of aspiration pneumonitis,[4] and a nearly 2% mortality rate.[5] The emergency physician's role is to terminate seizure activity, determine any underlying causes, and address these to minimize morbidity and mortality.[6]

Drug- or toxin-induced seizures result from exposure to or withdrawal from a medication, recreational drug, or toxin. Drug and toxin ingestions are an important cause of seizure activity that requires rapid identification and treatment by the emergency physician. It is estimated that 6.1% of new-onset seizures are drug-related.[7] In a study of 154 cases of status epilepticus from a county hospital setting, nearly 10% were due to substance ingestion, and 25% were ethanol-related.[8] Forty percent of these were unresponsive to initial therapy with benzodiazepines or phenytoin. Another study revealed that nearly 35% of the deaths associated with status epilepticus were due to drug- or alcohol-related seizures.[9] Seizures are a risk factor for poor prognosis, aspiration, and mortality in the overdose population.[4,10]

Generalized seizure activity may be the presenting symptom of some toxic ingestions or a preterminal manifestation of serious toxicity. Drug-induced seizures may occur as a primary manifestation of the effects of the toxin on the central nervous system (CNS) or as a secondary manifestation. Agents such as ethanol and benzodiazepines cause seizures from withdrawal states. This article will discuss the causes, pathophysiology, and treatment of substances that act directly on the CNS to cause seizures. Further, it will describe selected substances and drug classes in detail.

Epidemiology

There are no clear data regarding the epidemiology of drug- and toxin-induced seizures, as the diagnosis often is elusive and under-reported. Many patients with drug-induced seizures may not present to the ED with a clear history of ingestion or substance abuse. In a study of 204 patients in status epilepticus (SE), ethanol-related seizures were responsible for 13%, and drug overdose was responsible for less than 5% of SE. The case fatality rates in these patients were approximately 20% and 25%, respectively.[9] A retrospective review of the California Poison Control System data for 2003 found the leading causes of drug-induced seizures were bupropion (23%), diphenhydramine (8.3%), tricyclic antidepressants (TCA) (7.7%), tramadol (7.5%), amphetamines (6.9%), isoniazid (5.9%), and venlafaxine (5.9%). (*See Table 1.*) In this study, the authors compared their data from 2003 with a similar investigation from 1993. They found an increase in antidepressant-related seizures but a decrease in the TCA- and cocaine-related seizures.[5] Of these cases, 68.6% involved a suicide attempt, and 14.8% were the direct result of drug abuse. Pesola et al. determined 6.1% of all new-onset seizures (excluding alcohol withdrawal) at a single center over a five-year period were drug-related. Of the 279 cases of new-onset generalized seizures, alcohol withdrawal accounted for 17.6%.

Executive Summary

- **Drug- or toxin-induced seizures should be considered in any patient with seizures of unknown origin or in patients with seizure activity and known overdose.**
- **Seizures in the setting of overdose are an independent predictor of mortality.**
- **Standard care with attention to the ABCs for undifferentiated seizures should be undertaken, with up to 0.1 mg/kg IV of lorazepam as the first-line treatment.**
- **If known overdose and seizures co-exist, specific treatment and antidotes should be initiated immediately.**

The most common associations with drugs included cocaine (2.2%), benzodiazepine withdrawal (1.8%), and bupropion (1.4%).[7]

Pathophysiology

Seizures result from unorganized electrical discharge in the brain. This may manifest as a range of symptoms from altered mental status without convulsions, to partial seizures without alteration of consciousness, or generalized convulsive motor activity. Drug-induced seizures usually involve both cerebral hemispheres and therefore result in loss of consciousness with generalized abnormal motor activity. While not all the pathways are elucidated or are completely understood, some basic principles and knowledge of the important neurotransmitters involved in the pathogenesis of seizures are useful for understanding treatment. Typically, seizure activity occurs when there is a sudden imbalance between the excitatory and inhibitory forces within the cerebral cortex, leading to uncontrolled neuronal stimulation.

The initial factor that triggers seizure propagation is not always clear. Once sensitive neurons initiate local hyperpolarization, recruitment of other neurons follows. When the hyperpolarization extends to the reticular activating system and deeper structures of the brain, level of consciousness is affected. Seizures may occur because of sustained firing of the sodium channel, excessive calcium conductance, or an imbalance between excitatory and inhibitory neurotransmitters. The primary neurotransmitters involved are acetylcholine, gamma-aminobutyric acid (GABA), and glutamate. Periodic oscillations of these neurotransmitters occur in the thalamicocortical circuit and are regulated by serotonergic, noradrenergic, and cholinergic brainstem pathways.[11]

The main inhibitory neurotransmitter of the CNS is GABA. Typically, when GABA receptors are stimulated, they inhibit membrane depolarization.[12] Inhibition or depletion of GABA increases membrane depolarization and may result in seizures.[13] This depletion occurs in the setting of isoniazid overdose.[14]

Glutamate is the main excitatory neurotransmitter. Three main receptors mediate the effect of glutamate release: NMDA, AMPA/kainite, and metabotropic. Glutamate binds to receptors causing influx of sodium, calcium, or both, which, in turn, causes neuron depolarization. Increased excitation is also caused by increased synchrony between neurons.[15,16] One of the effects of chronic ethanol use is an increase in NMDA receptors. When ethanol use ceases suddenly, the increased neuroexcitatory tone is unmasked and may trigger seizures.

Autonomic overstimulation can occur as a direct or indirect effect of drugs. Similarly, cholinergic overstimulation may result in seizures as is seen with exposure to cholinesterase inhibitors such as organophosphate pesticides or nerve agents.[17] Adenosine receptors also are implicated in convulsive activity.

Drug-induced seizures may occur as a primary manifestation of the effects of the toxin on the central nervous system (CNS) or as a secondary manifestation. Secondary seizures are seizures caused indirectly by the effects of a substance on the body via metabolic perturbations such as sulfonylurea drugs via hypoglycemia, narcotics via hypoxia, MDMA via hyponatremia (as well as other mechanisms), and salicylates via cerebral edema. Treatment of secondary seizures often is based on correcting the primary disturbance (e.g. oxygenation, electrolyte replacement, glucose,etc.).

Factors contributing to drug-induced seizures include intrinsic epileptogenicity of the substance, dose, route, and CNS levels. Substances with high lipid solubility, low molecular weight, low protein binding, and weakly polar are more likely to penetrate the CNS. Patient factors predisposing to seizure include underlying epilepsy, neurologic abnormality, reduced drug clearance (liver failure, renal insufficiency, older age), and breakdown of the blood-brain barrier. Although the potential list of substances that can induce seizures is enormous, Table 2 lists many

Table 1: Common Causes of Drug-Induced Seizures

• Bupropion	23%
• Other	12%
• Antidepressants — other	9%
• Dyphenhydramine	8%
• Tramadol	8%
• Tricyclic antidepressants	8%
• Amphetamine	7%
• Isoniazid	6%
• Venlafaxine	6%
• Antipsychotic	5%
• Cocaine	5%
• MDMA	3%

Source: Thundiyil JG, Kearney TE, Olson KR. The evolving epidemiology of drug induced seizures reported to a poison control center system. *J Med Toxicol* 2007;3:15-19.

Table 2: Drugs or Toxins That May Cause Seizures

Drugs of Abuse
- Cocaine
- Amphetamines
- MDMA
- Phencyclidine (PCP)
- Ketamine

Natural Substances
- Water hemlock (*Cicuta douglasii*)
- Gyromitra esculenta mushroom
- Jimson weed (*datura stramonium*)
- Ephedra

Anti-epileptics
- Phenytoin/fosphenytoin
- Carbamazepine
- Lamotrigine
- Tiagabine
- Vigabitrin
- Analgesics
- Propoxyphene
- Tramadol
- Mefenamic acid
- Salicylates
- Meperidine
- Phenylbutazone

Antidepressants and Antipsychotics
- Tricyclic antidepressants
- Citalopram
- Escitalopram
- Bupropion
- SSRI
- Venlafaxine
- Lithium
- Chlorpromazine
- Phenothiazines
- Clozapine
- Olanzapine
- Quetiapine

Miscellaneous Agents
- Methylxanthines (theophylline)
- Isoniazid
- Anticholinergics (diphenhydramine, doxylamine)
- Organochlorine pesticides
- Lindane
- Camphor
- Local anesthetics
- Organophosphate pesticides
- Carbamates
- Nerve agents
- Chloroquine
- Quinine
- Asphyxiants
- Methyl bromide
- Iron

Withdrawal
- Ethanol
- Baclofen
- Sedative-hypnotics
- GHB

substances frequently implicated in drug-induced seizures.

Clinical Presentation of Drug- and Toxin-Induced Seizures

Seizures may occur after therapeutic use of antibiotics, analgesics, cardiovascular agents, antipsychotics, sympathomimetics, or herbal remedies. They also may occur after exposure to plant toxins or hydrocarbons. However, most drug-induced seizures occur after intentional overdose of medications, abuse of illicit drugs, or withdrawal from ethanol or sedative/hypnotics.[5] The recognition of these categories and associated toxidromes is important in the ED because seizures may herald the onset of life-threatening instability.

Differentiating drug- and toxin-induced seizures from other causes can be difficult and initially may be irrelevant. Without a history of known seizure disorder or of specific overdose, there are few "screening" tests to help narrow the differential diagnosis. Physicians must use all available resources to obtain an adequate history to help delineate the origin of seizures and possible causative agents if drug-related.

Specific clinical presentations may help to narrow the differential and guide treatment. If there is no known history of epilepsy, and the patient is not hypoxic or hypoglycemic, the clinician should maintain a high index of suspicion to consider drugs or toxins as the etiology. Conversely, if the seizure is focal, lacks alteration in level of consciousness, or lacks a post-ictal period, then the seizure is unlikely to be drug-related.

If there is suspicion for drug-induced seizures, certain historical or clinical clues can prove useful. Assess the patient's access to medication. A sympathomimetic toxidrome preceding seizure activity may suggest stimulant or drug withdrawal. Seizures associated with a prolonged QRS on ECG may be a clue to TCA, propoxyphene, venlafaxine, or diphenhydramine overdose. A past medical history of tuberculosis or epilepsy may suggest isoniazid (INH) or tiagabine, respectively. Putting the entire clinical picture together is important in narrowing the differential for drug- and toxin-related seizures and potentially leading to an agent-specific treatment. Serum levels of certain medications or toxins may be useful, and occasionally drug screens may help clarify a clinical picture. Complications associated with seizures may include respiratory depression, cardiac dysrhythmias, self-injury, hypotension, hypertensive crisis, hyperthermia, aspiration pneumonia, rhabdomyolysis, neuronal damage, anoxic brain injury, and death.[18] In addition to seizure termination, the emergency physician's role is to provide supportive care and airway management, and to anticipate and prevent complications.

General Approach to a Seizing Patient

Differential Diagnosis. Determining whether a patient is

having a "true" seizure is the first differential consideration when faced with a patient who "seized." Ictal activity can be irrefutably confirmed only by electroencephalography (EEG). Other diagnoses such as syncope, hyperventilation syndrome, toxic or metabolic disorders, and non-ictal CNS events such as a hemiparetic migraine or transient ischemic attack need to be considered. (*See Table 3.*) In general, ictal tonic-clonic activities are more forceful, prolonged, and associated with a post-ictal period as opposed to the "twitches" or fasciculations associated with fainting. If it is still unclear whether a true seizure, syncope, or pseudo-seizure occurred, a prolactin level may be useful. Elevated prolactin levels within 20 minutes of a suspected true seizure can be effective in differentiating a true seizure from a psychogenic seizure. However, a prolactin level does not differentiate an epileptic seizure from syncope.[19]

Initial Assessment and Stabilization. A patient who arrives at the emergency department with a history of possible seizure activity should be placed in a monitored area and should have intravenous access established. Initial management should focus on airway protection, oxygenation, circulatory support, and rapid bedside glucose determination. Most seizures are brief and will end by the time a patient reaches the ED. Status epilepticus is variably defined but is most often defined as a continuous seizure lasting longer than 30 minutes or recurrent seizures without a lucid interval over the same period. Seizures lasting more than 5 minutes initiate neuronal damage and are likely to progress to status epilepticus and should therefore be treated early and aggressively.[20]

If the patient is actively seizing in the ED, attend to the ABCs initially. In particular, one must confirm that the "seizure" is not the result of cerebral hypoxia from hypoperfusion. Traditionally, clinicians are taught to roll a patient on his or her side to protect the airway from aspiration. However, in one recent study, the authors found a greater risk for self-injury, particularly shoulder dislocation, during a major motor seizure when patients were rolled onto their side.[21] Gastric decontamination is not warranted in this population due to the risk of aspiration in the setting of seizures. Similarly, activated charcoal is not advisable for patients who have already seized or who have ingested a substance that may cause seizures.

Table 3: Differential Diagnosis for Convulsions

Metabolic
- Acute intermittent porphyria
- Febrile seizure
- Hepatic encephalopathy
- Hyperglycemia
- Hyperthyroidism/thyrotoxicosis
- Hypernatremia
- Hypocalcemia
- Hypoglycemia
- Hypomagnesemia
- Hyponatremia
- Hypoxemia
- Hypothyroidism
- Uremia

Cardiac
- Low cardiac output/hypoxia
- Convulsive syncope

Vascular
- Arteriovenous malformation
- Carotid sinus hypersensitivity
- Embolic
- Intracerebral hemorrhage
- Hypertensive encephalopathy
- Subarachnoid hemorrhage
- Thrombotic
- Vasculitis

Infectious
- Brain abscess
- Creutzfeldt-Jakob disease
- Encephalitis
- HIV encephalopathy
- Meningitis
- Neurosyphyllis
- Tetanus

Intracranial
- Brain mass/tumor
- Cerebral edema
- Traumatic brain injury

Autoimmune Disease
- Cerebritis
- Multiple sclerosis

Degenerative
- Alzheimer's disease
- Pick's disease

Movement Disorders
- Hemiballism
- Tics

Ideopathic
- Epilespy
- Paroxysmal dyskinesia

Pregnancy-related
- Eclampsia

Psychiatric
- Fugue state
- Panic attacks
- Pseudoseizure

CNS
- Hemiparetic migraine (Todd's paralysis)
- Narcolepsy

Pharmacotherapy

Hypoglycemia is the most common metabolic cause of seizure activity and should be treated appropriately with a 50 mL bolus of D50.[22] If seizure activity persists, initiate treatment with benzodiazepines. Due to its rapid onset of action and effective half-life in the brain, lorazepam is the benzodiazepine of choice. Based on review of multiple randomized double-blinded studies, up to 0.1 mg/kg IV lorazepam is recommended as first-

Table 4: Treatment for Drug-Induced Seizures

Drug	Adult Loading Dose	Comments
Lorazepam	Up to 0.1 mg/kg IV at 1-2 mg/min	First-line for most seizures Monitor airway closely.
Pyridoxine	5 g IV for unknown ingestion OR 1:1 for amount ingested	Consider as second-line agent if unknown substance ingested or if known isoniazid, rocket fuel, or mushroom exposure.
Phenobarbital	10-20 mg/kg IV at 60-100 mg/min	Use if persistent seizures despite benzodiazepine treatment or persistent seizures with TCA, theophylline, INH, local anesthetic, or lindane exposure. May require intubation.
Fosphenytoin	15-20 mg PE/kg IV at 100-150 mg/min	Monitor airway. Fewer side-effects than phenytoin IV. May be less beneficial than phenobarbital for drug-induced seizures. Acceptable second-line if status epilepticus (SE) of unknown cause. Dosed in phenytoin equivalent (PE) units.
Valproate	20 mg/kg PR or 10-15 mg/kg IV	Maximum dosage is 60 mg/kg/day. Onset is slow. Consider for refractory SE.
Propofol	1-2.5 mg/kg IV	Maintenance infusion 20-100 mcg/kg/min.

line therapy for control of status epilepticus.[23,24] Benzodiazepines can cause respiratory depression and may necessitate airway intervention.

If seizures persist despite adequate doses of benzodiazepines, the optimal second agent is controversial and may depend on the substance ingested. In the setting of ethanol-related seizures, phenytoin lacks efficacy.[25-27] Similar results exist in the setting of seizures induced by TCAs,[28] theophylline, isoniazid, local anesthetics,[29] and lindane.[30] Phenytoin has the potential to exacerbate cardiac conduction abnormalities in the setting of overdose.[29,31] Additionally, some studies suggest that, as a single agent, phenobarbital is more effective than phenytoin in the treatment of generalized (not drug-induced) status epilepticus.[32] For these reasons, many authors recommend phenobarbital up to 20 mg/kg IV as the second-line agent in the setting of drug-induced seizures. If it is unclear whether the seizure is drug-induced or what substance was involved (e.g., not ethanol, TCA, theophylline, INH, or lindane), it is reasonable to consider administration of fosphenytoin. Although IV phenytoin is less expensive, fosphenytoin is advantageous because it can be loaded faster and does not carry the risk of "purple glove syndrome," which is pain, edema, and discoloration to the limb after extravasation of IV phenytoin.[33] The loading dose is 15-20 mg PE/kg of phenytoin equivalents. Another dose of 5-10 mg PE/kg may be administered if the initial loading dose is ineffective. Seizures that remain unresponsive should be treated with intravenous pyridoxine 5 g for the possibility of isoniazid-induced seizures. (*See Table 4.*) Table 5 summarizes the common medications and doses for the treatment of SE.

Refractory status epilepticus provides a treatment dilemma, as there are no prospective clinical trials on the subject. Multiple agents are recommended, including midazolam, propofol, high-dose pentobarbital, valproate, topiramate, tiagabine, ketamine, and isoflurane. The preferred mode of treatment currently is IV infusion of midazolam or propofol with continuous EEG monitoring.[27,34,35] In this situation, the patient will need definitive airway protection. Continuous neuromuscular blockade is required to facilitate intubation in patients who continue to seize. In the setting of pharmacologic paralysis, continuous EEG monitoring is essential to determine response to antiepileptic therapies. Neurology consultation should be obtained on any patient with status epilepticus or refractory seizures. The following sections describe specific substances with higher complications, unique treatment algorithms, or frequent incidence of seizures.

Table 5: Specific Treatment or Concerns for Drugs or Toxins Described in this Paper

Drug or Toxin	Treatment
Stimulants (cocaine, amphetamines)	Benzodiazepine
Isoniazid	Pyridoxine (1:1 for ingestion of known amount, 5 g if unknown amount and repeat as needed)
Mushrooms (false morel)	Pyridoxine (5 g)
Organophosphates	Atropine, benzodiazepines
Nerve agents (Saran, Soman)	Atropine
Lithium	Hemodialysis
Theophylline	Hemodialysis, barbiturates, and beta blockers
Tricyclic antidepressants	Sodium bicarbonate, hypertonic saline, barbiturates, norepinephrine. Avoid physostigmine or phenytoin.
Citalopram/escitalopram	Electrolyte correction, magnesium replacement
Venlafaxine	Intravenous fluid and monitor for rhabdomyolysis
Baclofen	Baclofen and dantrolene
MDMA	Fluid restriction, electrolyte correction
Antipsychotics	Physostigmine for agitated delirium
Carbamazepine	Hemodialysis and charcoal hemoperfusion
Lamotrigine	Sodium bicarbonate for widened QRS
Tiagabine	EEG monitoring for non-convulsive status epilepticus
Anticholinergic (diphenhydramine, doxylamine)	Physostigmine for agitated delirium
Local anesthetics	Intravenous lipid emulsion therapy
Tramadol	Avoid narcan
Propoxyphene	Sodium bicarbonate for widened QRS
Water hemlock	Hemodialysis

Specific Substances. Stimulants. Stimulants (such as cocaine, amphetamines, MDMA) cause an increase in norepinephrine and serotonin that may be responsible for their proconvulsant effects.[36] Although the percentage of cases of seizures associated with stimulants decreased from 1993 to 2003, stimulant-induced seizures are associated with a higher mortality rate.[5] Despite this decrease in percentage of stimulant-related cases, the actual number of cases remains the same, and there is an increasing number of MDMA- and methamphetamine-associated seizures during the same time frame.[37] A hyperadenergic state (evidenced by hypertension, tachycardia, diaphoresis, or mydriasis) should alert the clinician to the diagnosis. Treatment includes intravenous fluids, evaporative cooling if hyperthermic, supportive care, and monitoring for rhabdomyolysis. Benzodiazepines are the first-line treatment for both the autonomic signs and symptoms and the seizure activity associated with stimulant abuse. In a case series of deaths attributed to drug-induced seizures, the authors determined 3 out of 7 deaths to be due to stimulant abuse.[5] In each case, the patients presented with seizures and hyperthermia, and two-thirds of the patients were "body stuffers." For this reason, it is important for clinicians to maintain vigilance for complications in the setting of seizures and hyperthermia, stimulant abuse, or body stuffers. This finding is consistent with animal studies, which reveal that hyperthermia in the setting of methamphetamine use and seizures results in degeneration of the blood-brain barrier and hippocampal damage.[38] Further, since hyperthermia aggravates neuronal injury, it is important for the ED physician to control temperature in the setting of seizures via seizure control, evaporative cooling, and paralysis.[39]

Cocaine use stimulates the release of norepinephrine as well as serotonin.[40] At high doses, it produces cardiovascular complications, seizures, and death.[41] Cocaine toxicity leads to more than 125,000 emergency visits annually, accounting for about 20% of all those seeking emergency care for drug-related complaints.[42] Cocaine can trigger seizures in patients with epilepsy and accelerate seizures in alcoholic patients undergoing detoxification.[43,44] In a study of 474 patients with cocaine intoxication, 7.9% of those with no previous epilepsy had seizures triggered by cocaine. While most seizures are brief and self-limited, patients who had seizures that were focal, multiple, or induced by nasal cocaine use were more likely to experience an acute intracerebral complication.[45] Cocaine-induced seizures also may trigger lactic acidosis and hyperthermia. Treatment for autonomic signs and symptoms as well as associated seizures should include aggressive cooling and use of benzodiazepines.[19,46] Cocaine also can cause cardiotoxicity, including widened QRS. This should be treated with intravenous sodium bicarbonate. There is currently no single agent that reverses all of the effects of cocaine. ED treatments aim to minimize the effects of cocaine toxicity.[47] However,

recent animal studies show promising results using a bacterial cocaine esterase to enhance the degradation of circulating cocaine, prevent seizures, and decrease mortality.[44]

Similar to cocaine, amphetamine and amphetamine analogues (e.g., MDMA, ephedra) induce release of norepinephrine and serotonin. The duration of convulsive activity is longer for amphetamines than for cocaine. Amphetamine-triggered seizures are less common than cocaine-triggered ones; however, a single dose of amphetamines or analogous substance (e.g., ephedra) can trigger single or multiple seizures.[48] Banned in 2003 by the U.S. Food and Drug Administration, ephedra was reported to cause seizures in 7 of the 140 adverse outcomes reported in the *New England Journal of Medicine* in 2000.[49] The hallucinogenic amphetamines such as MDMA possess a greater serotonergic effect.[19] Fatalities from MDMA are directly correlated with number of seizures.[50] Amphetamines are reported to be the fifth leading cause of drug-induced seizures due to their direct effects via serotonin and indirect effects of hyponatremia.[5] The hyponatremia seen with amphetamine abuse is caused by both excess antidiuretic hormone production and increased water intake.[51] In this setting, electrolyte correction and withdrawal of the offending agent are critical for treatment of seizures.

Antidepressants. Psychotropic drugs reduce the seizure threshold and induce seizures at both therapeutic concentrations and in overdose. Incidence of seizures at therapeutic usage of antidepressants and antipsychotics range from 0.1-1.5%. In overdose, the risk increases to between 4 and 30%.[52] The risk for seizures and mortality induced by antidepressants appears to be highest after ingestion of amoxapine, dothiepin, or maprotiline.[53,54] Historically, most of these seizures occurred from exposure to TCAs,[55] with an incidence of 4-20% after overdose.[56] While studies demonstrate a decrease in tricyclic antidepressant-related seizures, there is an overall increase in the proportion of antidepressant-related seizures.[5,7]

TCAs. Although there is a declining incidence of TCA overdose, the fatality rate from overdose remains significantly higher when compared to other antidepressants.[57] TCA overdose carries a nearly 10% risk of seizures.[53] Seizures and decreased level of consciousness in the setting of TCA overdose are associated with cardiovascular deterioration and mortality.[58,59] TCAs possess a variety of pharmacological effects, including sodium channel blockade, antihistaminic properties, anti-muscarinic properties, alpha blockade, GABA inhibition, and inhibition of serotonin and norepinephrine reuptake. This may cause symptoms of hypotension, anticholinergic toxicity, cardiotoxicity, coma, and seizures.

While the QRS width does not always predict toxicity,[60] there appears to be a correlation with seizures regarding most TCAs in the overdose setting.[60] In one study, there was a 34% incidence of seizures when the limb lead QRS exceeds 0.10 seconds.[61] Meanwhile, no seizures occurred in patients with a QRS < 0.1 seconds. In another study, the R wave in lead aVR was greater in patients who had seizures or arrhythmias than in those who did not.[62] Buckley et al. compared ECG findings in TCA overdose patients with arrhythmias to other psychotropic drug overdoses and found that TCA overdose patients were more likely to have an R wave in aVR, wider QRS, and longer QTc.[63] A recent meta-analysis of 18 studies examining the predictive value of QRS width revealed that QRS width had a sensitivity and specificity for predicting seizures of 0.69 and 0.69, respectively. The same study revealed that the sensitivity and specificity of QRS width to predict ventricular arrhythmia and mortality were 0.79 and 0.46, and 0.81 and 0.62.[64]

One study of TCA-induced seizures revealed that seizures usually are generalized, brief, and occur within 1.5 hours of ingestion. However, sustained seizures may occur in up to 17% of TCA overdoses. Mortality may be as high as 10% for TCAs in the setting of seizures.[65] Another study revealed that QRS widening and hypotension immediately follow seizures in 41% and 29% of cases, respectively.[66] Flumazenil and physostigmine have both been reported to induce seizures in this setting and should therefore be avoided in these patients.[67]

Supportive care is important for the treatment for tricyclic antidepressant poisoning. There does not appear to be a beneficial effect from treatment with phenytoin.[68] Rather, treatment of seizures, as they occur, with benzodiazepines, barbiturates, and propofol may be more beneficial. If seizures fail to respond to these modalities, neuromuscular paralysis should be considered. Sodium bicarbonate boluses appear to be beneficial for treatment of hypotension and cardiotoxicity.[69] in animal models, hypertonic saline is beneficial in this setting, but its use is not well studied in humans. The use of amiodarone in the setting of a tricyclic antidepressant-induced wide complex tachycardia is not adequately studied but does not appear to produce a benefit.[70,71] In a recent animal study, lipid emulsion therapy demonstrated significant reversal of clomipramine-induced hypotension when compared with sodium bicarbonate.[72] In the setting of refractory hypotension, pressors such as norepinephrine may be used.

Bupropion. Bupropion is a monocyclic antidepressant that inhibits dopamine and norepinephrine reuptake. It was initially withdrawn from the U.S. market in 1986 due to safety concerns and seizures but was later reintroduced and by 2007 was the fourth most commonly prescribed antidepressant in the country.[60] While most newer antidepressants actually decrease the rate of seizures among patients taking antidepressants, bupropion increases the seizure rate.[73] In fact, it was recently demonstrated that bupropion is the most common cause of drug-induced seizures, accounting for a significant portion of new-onset seizures presenting to the emergency department.[5] A retrospective study demonstrated that even an extra dose of bupropion doubles the risk for seizure.[74] The incidence of seizures is

dose related, with a seizure rate of: 18% for 0-4.5 g ingestions, 50% for 4.6-9 g, and 100% for > 9 g.[75] In studies of bupropion overdoses, the seizure incidence ranges from 11-15%, and this rate was highest among those taking an extended-release preparation.[76,77] In a recent study of 117 patients who overdosed on extended-release bupropion, nearly one-third developed seizures. Predictors for seizures included agitation, tremors, and tachycardia.[78] A significant number of patients experienced seizures greater than 8 hours post-ingestion. Consequently, patients who overdose on extended-release bupropion should be observed for a minimum of 24 hours. In a study of nearly 7400 bupropion exposures, seizures are noted to be mostly single and self-limited; however, multiple seizures or status epilepticus in up to 5% of exposures and death are reported in overdose settings.[77] Additionally, other findings such as altered mental status, agitation, coma, cardiac conduction disturbances, and hypotension may be present and complicate treatment. Cardiotoxic effects from bupropion include conduction disturbances, prolonged QT interval, and widened QRS.[79] Widened QRS is best treated with intravenous sodium bicarbonate boluses. No specific antidote or treatment modality is recommended for bupropion-related seizures other than supportive care and aggressive use of benzodiazepines.

Citalopram and Escitalopram. Citalopram is a selective serotonin reuptake inhibitor with antimuscarinic properties that is associated with seizures at a higher rate than other, newer antidepressants.[80] Seizures occur in 5-15% of overdose patients.[81,82] Studies suggest that the incidence increases with co-ingestants and has a dose-related response, but seizures may occur in the absence of co-ingestants or electrolyte abnormalities.[83] Citalopram is associated with an increase in QT intervals.[84] Overdose with escitalopram is associated with QT prolongation, sedation, bradycardia, and hypotension.[85] Treatment includes seizure precautions and cardiac monitoring for as long as 24 hours after ingestion.

Venlafaxine. Venlafaxine is an atypical antidepressant that inhibits the reuptake of norepinephrine and serotonin, and indirectly inhibits dopamine. At therapeutic doses, seizures occur in 0.26% of patients taking this drug.[84] In overdose, it has a dose-dependent proconvulsant effects with up to a 14% incidence of seizures.[83,86] Doses of 900-1500 mg are associated with seizures.[87] Venlafaxine also is associated with rhabdomyolysis in the overdose setting with or without the presence of seizure activity.[88-90] Additionally, there is potential for cardiac toxicity, including QT and QRS prolongation and myocardial infarction.[91-93] In a recent study of 235 venlafaxine ingestions, tachycardia, hypertension, and QTc prolongation were identified as dose-dependent cardiovascular effects associated with overdose.[94] Similarly, Isbister identified tachycardia in 54%, hypertension in 40%, QRS >120 ms in 7%, and QT prolongation in 6% of venlafaxine overdoses.[95] Other clinical effects from overdose include nausea, vomiting, dizziness, hyperthermia, and CNS depression. Treatment includes aggressive supportive care, treatment of seizures with benzodiazepines, and close monitoring for delayed rhabdomyolysis, especially in patients who develop seizures. Consider sodium bicarbonate for widened QRS intervals.

Antipsychotics. *First-generation Antipsychotics.* First-generation antipsychotics are also known as typical antipsychotics or neuroleptics. These include fluphenazine, haloperidol, chlorpromazine, molindone, thiothixene, thioridazine, trifuoperazine, loxapine, perphenazine, prochlorperazine, pimozide, and zuclopenthixol. While the limiting side effect of this category of drugs involves tardive dyskinesia and movement disorders, there is also a low incidence of seizures associated with these medications. After overdose, antipsychotic drugs are less likely to cause seizures than cyclic antidepressants and carry a seizure incidence of approximately 1%.[96] Although haloperidol is reputed to possibly reduce seizure threshold, animal studies suggest that haloperidol is much less proconvulsant when compared with some second-generation antipsychotics.[97] Of the first-generation antipsychotics, chlorpromazine is associated with the greatest proconvulsant activity, based on weak epidemiologic data.[98]

Second-generation Antipsychotics. The second-generation antipsychotics, also known as atypical antipsychotics, are a group of structurally unrelated medications that act by working on serotonin and dopamine receptors. Examples include clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, and paliperidone. The seizure incidence appears to be highest with clozapine and olanzapine. Studies suggest that 2.8% of patients treated with clozapine will experience seizures. This risk is dose-dependent, with a predicted cumulative 10% seizure risk after 3.8 years of treatment.[99] Other studies demonstrate EEG abnormalities in patients taking antipsychotics, most commonly with clozapine (47.1%), followed by olanzapine (38.5%), risperidone (28%), and typical neuroleptics (14.5%).[100]

Quetiapine overdose is associated with a seizure risk of approximately 2%.[101] Other clinical manifestations include drowsiness, coma, tachycardia, hypotension, respiratory depression, and QT prolongation.[102] Incidence of seizures, in one study, was no higher than other antipsychotics; however, the incidence of hypotension, coma, respiratory depression, endotracheal intubation, and death was found to be higher.[103]

A recent study suggests that second-generation antipsychotics carry significant toxicity when compared to older antipsychotics. In a retrospective cohort study of 1975 patients comparing adverse outcomes in first- and second-generation antipsychotics, second-generation antipsychotics were more likely to cause respiratory depression, coma, and hypotension in overdose.[104] This is likely caused by profound central nervous system depression. Other studies, however, suggest that the rate of cardiovascular toxicity is rare[105] and that second-

generation antipsychotics are relatively safe in overdose because they respond well to supportive treatment measures.[103] Treatment involves maintaining a patent airway, cardiac monitoring, treatment of hypotension with fluids and occasionally pressors, and benzodiazepines for seizures. Barbiturates may be preferable to phenytoin for treatment of refractory seizures.[106] Hypotension often is caused by alpha blockade (especially thioridazine) and should be treated initially with intravenous saline followed by norepinephrine, if needed. Widening of the QRS interval is more common in the setting of thioridazine or mesoridazine overdose and should be treated with sodium bicarbonate boluses. If anticholinergic-induced agitation is present (as may occur with overdose of clozapine, olanzapine, or quetiapine), physostigmine may be used if the ECG does not demonstrate evidence of QRS widening or other conduction disturbances.

Anti-epileptic Drugs. Ironically, a rare finding after anticonvulsant overdose is seizures. This clinical manifestation most commonly occurs after exposure to phenytoin, carbamazepine, vigabatrin, tiagabine, and lamotrigine.[107]

Tiagabine. Tiagabine is an anti-epileptic with relatively few side effects that selectively inhibits the reuptake of GABA. Despite its anti-epileptic effects, it induces nonconvulsive status epilepticus at therapeutic doses at a significantly higher rate (7.8%) than other anti-epileptics.[108] It causes both convulsive seizures and non-convulsive status epilepticus in the setting of overdose.[109] Non-convulsive status epilepticus often manifests as intermittent chronic confusional states but can progress to coma or death. Other symptoms associated with tiagabine overdose include lethargy, coma, confusion, agitation, tremors, dizziness, hallucinations, tachycardia, and respiratory depression. Seizures occur in a dose-related manner, especially after the ingestion of three times the maximal recommended daily dose.[110] Treatment for tiagabine is symptomatic, with use of benzodiazepines for seizures. Continuous EEG monitoring is helpful for diagnosis and treatment of non-convulsive status epilepticus.

Narcotics. Clinical presentation for opioid overdose includes mental status depression, respiratory depression, and typically miosis. In opiate abusers, there is an estimated 12.5% incidence of lifetime seizures.[111] According to the CDC, prescription drugs cause most of the more than 26,000 fatal overdoses each year. In fact, the number of overdose deaths from opioids alone more than tripled from 1999 to 2006, to 13,800 deaths per year.

Overdose of propoxyphene may present with decreased mental status, cardiotoxicity and seizures. Seizures occurred in as many as 20.2% of patients presenting with propoxyphene abuse.[112] Of these seizures, 87% were generalized tonic-clonic and typically occurred 2 hours after consumption. The treatment for these seizures is benzodiazepines, and the treatment for the widened QRS interval is intravenous sodium bicarbonate.[113]

Tramadol increases serotonin and norepinephrine in the synapse via reuptake inhibition.[114] Seizures occur not only in overdoses but also in therapeutic doses and are not dose dependent.[115] The incidence of seizures was found in one study to be 13.7% in patients taking tramadol, and chronic users appear to be more susceptible.[116] Conversely, seizure activity also has been reported when reversing the effects of tramadol by using naloxone.[117]

The metabolite of meperidine, normeperidine, is highly epileptogenic.[118] This can be seen with high doses or in patients with compromised kidney function. Normeperidine also is associated with delirium, dysphoria, tremor, and serotonin syndrome. The opioid effects of meperidine are reversed by naloxone.

Methylxanthines. Methylxanthines such as theophylline antagonize adenosine receptors and increase cAMP by inhibiting phosphodiesterase and stimulating beta-adrenergic activity.[119,120] Although there may be other mechanisms by which theophylline causes seizures, a recent animal study suggests that blockage of the adenosine A1 receptor is the main cause of theophylline-associated seizures (TAS).[121,122] A study of 399 cases of theophylline toxicity revealed that the most common clinical effects included nausea and vomiting (79%), tachycardia (75%), hypokalemia (28%), and seizures (27%).[123] Other common effects include tremor, anxiety, hypotension, and ventricular arrhythmias. Poisoning from theophylline may occur from acute overdose or chronic exposures. Seizures are more likely to occur with serum levels of greater than 100 mg/dL in acute exposures and 60 mg/dL in chronic toxicity, but have been reported at therapeutic or mildly elevated levels.[124] TAS are more likely to be prolonged and refractory to standard treatment than non-TAS. First-line therapy for TAS should include benzodiazepines. However, prompt use of barbiturates is recommended for refractory cases to avoid potential brain injury secondary to status epilepticus.[125] TAS may be resistant to benzodiazepines since theophylline antagonizes their effects. In animal models, phenytoin was not an effective treatment and was shown to actually lower the seizure threshold in one study.[126] Treatment of hypotension should include use of intravenous saline, phenylephrine, or in some instances a beta blocker such as esmolol. Beta blockers also are indicated for treatment of supraventricular tachycardia and ventricular dysrhythmias.[127] Additional treatment for severe theophylline toxicity should include enhancing elimination with activated charcoal and hemodialysis.[128] However, charcoal should not be given to a patient who is at risk for seizures without a protected airway. Dialysis may be indicated for theophylline toxic patients with levels > 90 mg/dL, seizures, refractory hypotension, or ventricular dysrhythmias.[129] Patients should be observed for at least 18 hours after ingestion for the potential of delayed toxicity.

Isoniazid/Mushrooms. Isoniazid in overdose causes a pyridoxine (vitamin B6) deficiency by inhibiting

pyridoxine phosphokinase, the enzyme that converts pyridoxine to active B6.[130,131] Activated pyridoxine is required to convert glutamic acid to GABA, the absence of which is thought to lead to seizures. INH also may inhibit the conversion of lactate to pyruvate, enhancing the lactic acidosis during seizures. Severe overdoses result in the classic triad of recurrent seizures, lactic acidosis, and coma.[132] A retrospective chart review looking at 52 cases of INH overdoses reported that seizures were found in 100%, CNS depression in 53%, vomiting in 45%, leukocytosis in 75%, metabolic acidosis in 29%, elevated hepatic enzymes in 21%, and elevated creatine phosphokinase (CPK) in 60%.[18]

INH-induced seizures may be refractory to other standard treatments but may rapidly respond to pyridoxine.[133] If INH exposure is suspected, pyridoxine should be administered at a dose equivalent to 1:1 for amount of INH ingested. If the dose of INH ingested is unknown, a 5 g IV dose of pyridoxine is recommended to start and repeated as needed. Very large doses of pyridoxine may be required, possibly exhausting the hospital's supply.[132]

Numerous mushrooms may cause seizures. The false morel mushroom (*Gyromitra esculenta*) possesses a similar mechanism to INH. It is metabolized into monomethylhydrazine, which is structurally similar to isoniazid and results in a functional depletion of vitamin B6 and GABA. Other symptoms include delayed gastrointestinal symptoms, hepatotoxicity, and renal toxicity.[134] Benzodiazepines remain first line; however, they may be ineffective as their anticonvulsant effects are dependent on GABA levels. Pyridoxine 5 g IV should be administered to convert glutamic acid into GABA and reverse the seizure activity.[122,123]

Anticholinergic Drugs. In two separate studies, anticholinergic drugs were reported to account for up to 10% of drug-induced seizures.[5,135] Diphenhydramine is the most commonly ingested anticholinergic agent. Diphenhydramine (Benadryl) is an antihistamine with anticholinergic and sedative properties.[136] In 2003 there were 28,092 human exposures reported to poison centers in the United States.[137] Diphenhydramine overdose can cause significant anticholinergic symptoms as well as QRS prolongation, QT prolongation, rhabdomyolysis, and seizures.[129] QRS widening in diphenhydramine overdose, akin to other sodium channel blocking agents, appears to respond to treatment with intravenous sodium bicarbonate.[138] Currently, benzodiazepines are considered first-line for both the agitation and seizures associated with antihistamine overdose. Recent studies suggest that physostigmine may be safer and more efficacious than benzodiazepines in anticholinergic overdoses for controlling agitation and reversing delirium.[139,140] A relative contraindication to physostigmine treatment is evidence of QRS widening on ECG or a history of a TCA co-ingestion.

Jimson weed (*Datura stramonium*) is a member of the nightshade family and a common weed in the United States. All parts of the plant are poisonous, as they contain the belladonna alkaloids atropine, L-hyoscyamine, and L-scopolamine, causing anticholinergic toxicity. Jimson weed is sometimes consumed for its hallucinogenic and euphoric effects, and toxicity usually is the result of intentional ingestion by teenagers.[140,141] Patients present with anticholinergic symptoms: mydriasis, blurred vision, photophobia, dry mouth, dry skin, extreme thirst, difficulty swallowing, hyperthermia, hypertension, seizures, confusion, and agitation.[142] Treatment for these patients who may present with seizures or other symptoms of anticholinergic syndrome is similar to that of diphenhydramine.[141]

Camphor. Camphor and phenol are household toxins that are available and subject to accidental ingestions. Camphor is an essential oil derived from plant products and is present in over-the-counter remedies such as BenGay, Campho-Phenique, and Vicks.[143] Camphor was previously found in mothballs, but since 1982 has been restricted by the U.S. FDA to < 11% in products intended for medicinal use. Recently, Khine et al. reported a cluster of camphor-induced seizures in children associated with imported or illegally sold camphor products.[144] Clinical manifestations include localized burns, ataxia, drowsiness, confusion, mental status depression, and seizures.[145,146] Seizures occur very soon after ingestion, and even small doses may be highly toxic to children. There are no antidotes for camphor intoxication, so care is supportive, focusing on airway protection and seizure management.[147] Seizures can be treated with benzodiazepines and barbiturates.

Local Anesthetics. Local anesthetics work through reversible binding of sodium channels and are typically injected subcutaneously, applied topically, or used for regional anesthesia by injection near selected nerve targets. Toxicity is typically due to inadvertent intravascular administration.[148] Toxicity can be seen when excessive doses are administered (> 4.5 mg/kg lidocaine). Peripheral nerve blocks carry the highest rates of toxicity with symptoms in approximately 0.075-0.1% of procedures.[149,150]

Local anesthetic toxicity includes both cardiovascular and neurological symptoms.[151] Mild toxicity can include lightheadedness, dizziness, disorientation, drowsiness, chest pain, shortness of breath, and palpitations. More severe or higher-dose symptoms can include CNS excitation followed by depression, muscle twitching, convulsions, respiratory depression, coma, and cardiovascular depression and collapse. Cardiovascular collapse due to local anesthetic toxicity, especially bupivacaine, generally is resistant to standard resuscitation efforts.[151]

Seizures often are self-limited and are successfully treated with benzodiazepines and barbiturates, but they may indicate impending cardiovascular collapse.[152] Recent investigation into intravenous lipid emulsion (IVLE) to treat local anesthetic toxicity demonstrates promise. Several successful case reports of IVLE resuscitation in the setting of cardiac arrest have paved the way for various animal studies.[153] Studies suggest that

pretreatment with IVLE increases the median lethal dose of local anesthetics, reduces the LD50 of bupivacaine,[154] and increases survival in the setting of cardiotoxicity.[153] Optimal dosing is still unknown, but current dosing regimens suggest Intralipid 20% at 1-2 mL/kg bolus followed by 0.25 mL/kg/min.[155]

Withdrawal

Many drugs induce seizures via withdrawal. The most well known of these substances are ethanol and sedative-hypnotics. Withdrawal of these drugs causes a decrease in $GABA_A$ stimulation and subsequent loss of NMDA receptor inhibition. The result is an increase in glutamate stimulation, excitatory neuronal action potentials, and a hyperadenergic state with potential for seizure activity.[156] Patients present with autonomic stimulation, tremor, delirium, hallucinations, and seizures.

In the setting of ethanol withdrawal, seizures typically are seen 6-48 hours after cessation of drinking.[157] The primary treatment is benzodiazepines. High doses of benzodiazepines may be required. For refractory cases, phenobarbital and propofol should be considered.[158-160] anti-epileptic medications such as phenytoin are ineffective for treatment of these seizures.[159]

For seizures caused by benzodiazepine withdrawal, the onset of symptoms is not as predictable due to varying half-lives and pharmacokinetics of the various agents.[161] Physical dependency can occur in as little as a few weeks.[162] Symptoms include anxiety, dysphoria, irritability, insomnia, diaphoresis, hallucinations, delirium, hypertension, and seizures. Acute withdrawal may present as a confusional state due to nonconvulsive status epilepticus.[163] Factors contributing to seizure risk include brain damage, alcohol addiction, underlying seizure disorder, dose, and duration of therapy.[164] Rapid cessation or reversal with flumazenil of acute overdose in a chronic user may precipitate seizure activity.[165] Benzodiazepine withdrawal seizures are best treated in a similar fashion to alcohol-related seizures.

Baclofen is a $GABA_B$ agonist that is often administered via pump. It causes hyperactivity of neuronal calcium channels when the pump malfunctions and there is an abrupt withdrawal of drug. Clinical presentation includes hypertension, fever, tachycardia, delirium, hallucinations, and seizures. Withdrawal typically occurs between 12-96 hours after cessation of the drug. Dependence can occur after as little as 1-2 months. Benzodiazepines and re-administration of oral baclofen are the treatment of choice.[166] For cases of refractory baclofen withdrawal, usually from intrathecal pump malfunction, muscle spasticity and hyperthermia can be treated with dantrolene, antispasmodics, and benzodiazepines.[167]

Additional Aspects

Multiple or refractory seizures in patients should prompt a search for other causes such as co-ingestants, electrolyte abnormalities, hypoglycemia, CNS infection, or intracranial pathology. Due to excessive muscle contraction, patients should be monitored for rhabdomyolysis and acidosis. Excessive muscle contraction with persistent seizures may induce hyperthermia and warrant neuromuscular paralysis. Risk factors for mortality in the setting of all causes of status epilepticus include duration of seizure, age, delay to treatment,[168] cerebrovascular disease, and anoxic brain injury.[169] For drug-induced seizures, a retrospective study suggests that the presence of hyperthermia and stimulant-induced seizures was associated with higher mortality.[5] For this reason, aggressive cooling measures, continuous rectal temperature monitoring, and neuromuscular paralysis should be considered. Continuous EEG monitoring should be initiated for patients who are paralyzed. Neurology consultation should be obtained for any patient with status epilepticus.

In a follow-up prospective study of drug-induced seizures, initial hyperglycemia, acidosis, hyperthermia, systolic blood pressure < 90 mmHg, and stimulant overdoses were associated with complications.[135] While hyperglycemia and acidosis may be general biomarkers for prolonged seizure activity, other factors may contribute to increased complications. Hyperglycemia may enhance neuronal injury in the setting of seizures. Further, prolonged acidosis may decrease protein binding of certain drugs (e.g., TCA, antipsychotics) and enhance their cardiotoxicity. For this reason, careful glucose and electrocardiographic monitoring is warranted. These indicators should alert the clinician to consider intensive care monitoring.

Disposition

Patients with drug-induced seizures should have strong consideration for admission to an intensive care unit (ICU). Substances that are particularly high risk include TCAs, alcohol withdrawal in the setting of delirium tremens, and theophylline toxicity. Stimulant exposure, status epilepticus, necessity of continuous EEG monitoring, or exposure to drugs that induce cardiovascular instability, QRS widening, severe acidosis, or hyperthermia likely will require ICU admission. Many substances such as TCA, antipsychotics, and INH will produce seizures within 6 hours of exposure. However, in overdose, certain substances such as extended-release bupropion, meperidine, and citalopram may present with delayed seizures 8 hours after ingestion. Since seizures are a risk factor for poor prognosis, aspiration, and death in the setting of overdose, admission is highly recommended.[4] However, since some drugs may cause a self-limited seizure without risk for status epilepticus, each case should be evaluated based on substance ingested, amount, and intent.

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Physician CME Questions

51. All of the following medications are known to cause primary drug-induced seizures *ex-cept*:
    A. tricyclic antidepressants
    B. acetaminophen
    C. tramadol
    D. diphenhydramine

52. A patient with a baclofen pump that has stopped working arrives after a seizure. What therapy should be initiated?
    A. benzodiazepines and baclofen
    B. haloperidol and fosphenytoin
    C. phenobarbital and carbamazepine
    D. propofol

53. IV fosphenytoin is considered a better alternative than phenytoin for IV administration because:
    A. It is more cost-effective.
    B. It can be loaded at a faster rate.
    C. It does not cause "purple glove syndrome."
    D. B and C
    E. All of the above

54. What is the most common drug implicated in drug-induced seizures?
    A. TCA
    B. isoniazid
    C. haloperidol
    D. bupropion
    E. citalopram

55. What treatment is necessary, in addition to benzodiazepines, for Gyromitra (false morel) mushroom toxicity?
    A. phenobarbital
    B. propofol
    C. pyridoxine
    D. haloperidol

56. Methylxanthines are thought to cause seizures by:
    A. antagonizing adenosine receptors and increasing cAMP by inhibiting phosphodi-esterase
    B. inhibiting pyridoxine phosphokinase
    C. inhibiting GABA reuptake
    D. inhibiting voltage-gated sodium channels

57. Which of the following is true regarding tricyclic antidepressants overdoses?
    A. Seizures, in this setting, are a good prognostic factor.
    B. QRS width > 0.10 is predictive of seizures.
    C. R wave in avR may be predictive of seizures.
    D. Intravenous sodium bicarbonate should be used to treat seizures.
    E. B and C

58. Seizures associated with tramadol are:
    A. seen with high doses only
    B. seen in withdrawal states only
    C. not dose-dependent
    D. not seen when tramadol is reversed by naloxone

59. A patient was witnessed to overdose on diphenhydramine. He presents with seizures refractory to benzodiazepines. His electrocardiogram is normal. Which of the following is the next best drug to use?
    A. physostigmine
    B. haloperidol
    C. sodium bicarbonate
    D. gabapentin

60. Which of the following anti-epileptics is associated with non-convulsive status epilepticus?
    A. valproic acid
    B. carbamazepine
    C. tiagabine
    D. gabapentin
    E. lamotrigine

CME Answer Key

51. B; 52. A; 53. D; 54. D; 55. C; 56. A; 57. E; 58. C; 59. A; 60. C

Correction

In the February 1, 2010 issue ("Complications of Prosthetic Heart Valves in the Emergency Department"), the last sentence in the section on emergent treatment on page 40 should read, "Warfarin will not reach therapeutic levels for several days and, consequently, is not useful in the emergency setting." To view and print a corrected copy of the issue, please visit www.emreports.com.

Emergency Medicine Reports

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Upon completion of this educational activity, participants should be able to:

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