Perspectives in Pharmacology

Experimental Treatments for Cocaine Toxicity: A Difficult Transition to the Bedside

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ABSTRACT

Cocaine is a commonly abused illicit drug that causes significant morbidity and mortality. Although there is no true antidote to cocaine toxicity, current management strategies address the life-threatening systemic effects, namely hyperthermia, vasospasm, and severe hypertension. Clinicians rely on rapid cooling, benzodiazepines, and α-adrenergic antagonists for management, with years of proven benefit. Experimental agents have been developed to more effectively treat acute toxicity. Pharmacodynamic approaches include antipsychotics that are thought to interfere with cocaine’s actions at several neurotransmitter receptors. However, these medications may worsen the consequences of cocaine toxicity as they can interfere with heat dissipation, cause arrhythmias, and lower the seizure threshold. Pharmacokinetic approaches use cocaine-metabolizing enzymes, such as butyrylcholinesterase (BChE), cocaine hydrolase (CocH), and bacterial cocaine esterase (CocE). Experimental models with these therapies improve survival, primarily when administered before cocaine, although newer evidence demonstrates beneficial effects shortly after cocaine toxicity has manifested. CocE, a foreign protein, can induce an immune response with antibody formation. When enzyme administration was combined with vaccination against the cocaine molecule, improvement in cocaine-induced locomotor activity was observed. Finally, lipid emulsion rescue has been described in human case reports as an effective treatment in patients with hemodynamic compromise because of cocaine, which correlates well with its documented benefit in toxicity due to other local anesthetics. A pharmaceutical developed from these concepts will need to be expedient in onset and effective with minimal adverse effects while at the same time being economical.

For at least 30 years, cocaine has remained a major public health concern. In 2010, there were 1.5 million cocaine users in the United States alone (Substance Abuse and Mental Health Services Administration, 2011). The molecular actions of cocaine are numerous and defy a simple treatment to mitigate its toxic effects. Cocaine use predisposes to diffuse central nervous system (CNS) excitation. It inhibits the transporter proteins responsible for the reuptake of epinephrine, norepinephrine, serotonin, and dopamine into presynaptic neurons, allowing repeated activation of the postsynaptic neuron through α- and β-adrenergic, serotonergic, and dopaminergic receptors (Williams and Lacey, 1988). However, cocaine’s toxic effects cannot simply be explained by reuptake inhibition, because other agents with similar effects on reuptake do not cause the same clinical manifestations as cocaine toxicity. Concentrations of glutamate and aspartate, excitatory amino acids, increase significantly in animals exposed to cocaine and may play a crucial role in acute toxicity and neuromodulation resulting in addiction (Smith et al., 1995; Kasanetz et al., 2013). Morbidity and mortality largely result from acute cardiovascular and neurologic complications. Hyperthermia, vasospasm, and severe hypertension are produced by catecholamine excess and psychomotor agitation. General management with rapid cooling and fast-acting benzodiazepines is usually sufficient to decrease the risk of permanent disability or death. α-Adrenergic antagonists and the potential use of calcium channel antagonists and sedatives have proven to be of clinical use when the first-line measures are inadequate. The numerous biochemical actions of cocaine with effects on various cellular receptors make development of an antidote difficult. Newer agents such as antipsychotics that antagonize dopamine receptors, enzymes-metabolizing cocaine, and vaccines against cocaine have been developed. Preliminary results hold promise, although significant barriers may prevent these therapies from achieving practical utility in acutely cocaine-toxic patients. In this article, we will review several recent advances in the treatment of acute cocaine toxicity and discuss the difficulties facing their clinical implementation.

ABBREVIATIONS: ALT, alanine aminotransferase; BChE, butyrylcholinesterase; BE, benzoylecgonine; CNS, central nervous system; CocH, cocaine hydrolase; CocE, bacterial cocaine esterase; EME, ecgonine methyl ester.
**Current Clinical Management**

**Cooling**

Among the most dangerous effects of cocaine toxicity is its ability to raise core temperature and cause life-threatening hyperthermia (Roberts et al., 1984; Daras et al., 1995). Emphasizing the dangerous relationship between cocaine-induced hyperthermia and mortality, there is a 33% increase in mean cocaine-related mortality on days where the ambient temperature is above 88°F (Marzuk et al., 1998). In addition to protein denaturation that occurs at elevated body temperatures, the cardiovascular system, which is likewise being stimulated by the sympathomimetic effects of cocaine, is further taxed to maintain cardiac output in the face of temperature-induced vasodilation. In this setting, rapid resolution of hyperthermia is of utmost importance. In a canine model of cocaine toxicity, limiting hyperthermia by reducing the ambient temperature to −5°C was more protective against mortality than prevention of acidosis with sodium bicarbonate, prevention of convulsions with antiepileptics, or inhibition of dopamine with a dopamine antagonist. Cocaine administration caused dogs to become more hypothermic at −5°C than a control group, indicating that cocaine may have an effect in enhancing the response to hyperthermia, which is actually protective (Catravas and Waters, 1981). In humans, cocaine-induced hyperthermia is mediated by increased locomotor activity (Rosenberg et al., 1986). As the ambient temperature rises, cocaine augments elevations in core temperature, attenuates cutaneous vascular conductance and sweating, and decreases the perception of elevated temperature (Crandall et al., 2002). Rats given intravenous cocaine have increases in brain temperature that do not correlate with temporal muscle temperature (Kiyatkin, 2013). Patients with cocaine-induced hyperthermia often recover if rapidly cooled (Menaker et al., 2011), although the risks of prolonged elevations of core body temperature include death and permanent neurologic disability. Ice water immersion and paralysis are useful (Roberts et al., 1984; Rosenberg et al., 1986), and data suggest cold water immersion is the most practical treatment modality, effectuating rapid cooling at a rate of about 0.2°C/min (Armstrong et al., 1996).

**Benzodiazepines**

Generalized suppression of central nervous system activity antagonizes the sympathomimetic effects of cocaine. In animal models of cocaine toxicity, sedation with a benzodiazepine increases the mean lethal and convulsive doses of cocaine (Guinn et al., 1980) and improves survival (Guinn et al., 1980; Catravas and Waters, 1981; Yuksel et al., 2013). Through their action on the γ-aminobutyric acid receptors in the amygdala and reticular activating system, benzodiazepines function as anxiolytics, sedatives, and antiepileptics. Additionally, benzodiazepines may enhance the effect of endogenous adenosine on the myocardium by inhibiting the nucleoside transporter responsible for adenosine reuptake with resultant coronary vasodilation from A_{2A} receptor agonism (Seubert et al., 2000). Benzodiazepines also relieve tachycardia, hypertension, and vasoconstriction, thereby decreasing the metabolic demands of the myocardium. Finally, when high doses of ligands to the translocator protein, formerly known as the peripheral benzodiazepine receptor, are administered in vivo to rabbits and ex vivo to rat and rabbit hearts, the area of myocardial infarction is decreased after an ischemic stress. The mechanism of protection is potentially reduced cardiac mitochondrial membrane permeability that results in decreased apoptosis and prevents release of mitochondrial cytochrome c (Leducq et al., 2003; Obame et al., 2007). Success using short-onset benzodiazepines such as midazolam or diazepam has been a cornerstone of the treatment of acute cocaine toxicity since the 1980s. Large human trials assessing their efficacy are lacking, but recent meta-analysis data demonstrate a 51.7% improvement in survival in cocaine-poisoned animals treated with benzodiazepines compared with animals receiving placebo (Heard et al., 2011). In humans, a beneficial effect of benzodiazepine treatment is best demonstrated for patients with cocaine-related chest pain. In randomized trials, patients treated with a parenteral benzodiazepine plus sublingual nitroglycerin had more rapid and substantial improvement in their subjective pain scores than those receiving nitroglycerin alone (Honderick et al., 2003). In addition, those who received benzodiazepines alone did no worse than those treated with only nitroglycerin (Baumann et al., 2000).

**Adrenergic Receptor Antagonists**

Cocaine inhibits norepinephrine reuptake in central presynaptic nerves. Excess norepinephrine causes stimulation of both α- and β-adrenergic receptors. Studies of β-adrenergic antagonists in acute cocaine toxicity have shown decreases in the mean convulsive and mean lethal cocaine doses in animals (Guinn et al., 1980) and worsened coronary vasoconstriction in humans (Lange et al., 1990). Clinically, the use of a β-adrenergic antagonist in an acutely cocaine toxic patient has resulted in death (Fareed et al., 2007). Alternatively, α-adrenergic antagonists, such as phentolamine, can mitigate the vasoconstrictive effects of cocaine toxicity, suggesting the mechanism is cocaine-induced elevation in α-adrenergic tone (Lange et al., 1989). Mean arterial pressure and coronary vasospasm can be relieved, reducing afterload and improve myocardial perfusion. The clinical use of phentolamine has resulted in the resolution of chest pain and electrocardiographic changes consistent with coronary ischemia (Hollander et al., 1992).

Finally, calcium channel antagonists and neuromuscular blockers have been used to treat refractory cases of cocaine toxicity. Myocardial injury due to cocaine-induced vasoconstriction was decreased with verapamil in a clinical trial (Negus et al., 1994). Although little clinical evidence exists supporting use in acute cocaine toxicity, the mechanism of action of calcium channel antagonists makes them a reasonable second-line agent. Neuromuscular blockade is the last resort in the treatment of hyperthermia and agitated delirium associated with cocaine toxicity. After paralysis, locomotor activity is abolished and behavior is controlled, allowing passive and active cooling and administration of benzodiazepines.

**Therapies Under Development**

**Pharmacodynamic Approaches**

Treatments that antagonize receptors stimulated by cocaine can be categorized as pharmacodynamic approaches to the treatment of cocaine toxicity. Among the antagonists
being explored are antipsychotics that affect multiple receptors where cocaine has actions.

**Antipsychotics.** The use of atypical antipsychotics in cocaine toxicity exploits their mechanisms as dopamine, serotonin, and muscarinic inhibitors. Animal studies show antipsychotics as a class increase survival by 27% over placebo (Heard et al., 2011). Olanzapine, specifically, is an antagonist at the dopamine D₁, D₂, muscarinic, and serotonin 5HT₂A receptors. In mice pretreated with olanzapine, only 10.5% developed irreversible cocaine toxicity (and were euthanized) compared with 46.2% of those pretreated with placebo (Heard et al., 2009). Ziprasidone, an antagonist at dopamine and serotonin receptors, reduces cocaine induced lethality in pretreated mice by 51% (Cleveland et al., 2005), although in a more recent investigation using similar doses, ziprasidone failed to prevent lethality but did delay the onset of seizure (Cleveland et al., 2007). There are concerns whether antipsychotics should be used at all in the setting of cocaine toxicity (Wu et al., 2008). Conflicting data exist regarding antipsychotics that may be agent or or species specific. In dogs, pimozide showed no benefit in convulsions or lethality compared with controls, although a group treated with chlorpromazine had improved mortality and a slight increase in the mean convulsive dose (Catravas and Waters, 1981). In a small cynomologus monkey trial, there was an increased mean convulsive dose and fewer convulsions in those treated with chlorpromazine compared with controls, but a greater proportion of subjects with convulsions compared with those treated with diazepam (Guinn et al., 1980). Additionally, haloperidol pretreatment in rats did not improve cocaine-induced mortality (Witkin et al., 1989). Associated anticholinergic effects causing impaired heat dissipation, decreased seizure threshold, and prolongation of the QT interval are all potentially catastrophic to a cocaine-toxic patient. We conclude, for now, that data are insufficient to support the use of antipsychotics for patients with cocaine toxicity.

**Pharmacokinetic Approaches**

Pharmacokinetic approaches to the treatment of cocaine overdose aim to prevent its entry into, enhance its diffusion from, and mitigate subsequent action within the CNS. This mechanism aims to neutralize or metabolize cocaine rather than countering its clinical effects. Examples of this approach are the use of cocaine metabolizing enzymes, vaccines, and lipid emulsion.

**Enzymes.** Cocaine metabolism is complex. In addition to spontaneous hydrolysis, in humans, liver carboxylesterase hydrolyzes the methyl ester of approximately 45% of cocaine to form benzoylecgonine (BE) and butyrylcholinesterase (BChE) hydrolyzes the benzoyl ester of 45% of cocaine to produce ecorgonine methyl ester (EME). Approximately 5% of cocaine also undergoes N-demethylation by BChE to form norcocaine (see Fig. 1) (Dean et al., 1991). In isolated cerebral arteries from cats and fetal sheep, BE was a more potent vasoconstrictor than cocaine, norepinephrine, and norcocaine. EME actually demonstrated vasodilatory properties and was protective in mice (Madden and Powers, 1990). Norcocaine easily crosses the blood-brain barrier, whereas BE and EME are more restricted. Findings of BE in the brains of cocaine users days after last exposure, together with cocaine’s short half-life and clinical effects that last hours, suggest that cerebrovascular effects may be due to BE (Madden and Powers, 1990).

Three enzyme types have been studied as potential antidotal therapies to acute cocaine toxicity. Wild-type human BChE, also referred to as pseudocholinesterase, hydrolyses cocaine to EME (Misra et al., 1975). In humans, decreased BChE activity is associated with life-threatening reactions to cocaine, and it has been postulated that phenotypes with low BChE activity are more susceptible to cocaine (Hoffman et al., 1992). In rats pretreated with BChE and then exposed to cocaine, blood pressure elevation was mitigated and the lethal dose was increased. In rats administered cocaine 80 mg/kg...
and then given BChE 3 minutes later, a smaller proportion suffered convulsions or expired in a dose-dependent manner than controls (Lynch et al., 1997). After cocaine administration, a pretreated rat had significantly decreased plasma concentrations of cocaine, BE, and norcocaine and significant increases in EME compared with a control (Collins et al., 2011, 2012). Similar results are reported in pretreated squirrel monkeys in vivo and human plasma in vitro (Carmona et al., 2000). Interestingly, rat brain concentrations of cocaine and BE were not altered by BChE, although brain EME concentrations were increased in a dose-dependent manner after BChE pretreatment (Carmona et al., 2005).

A major limitation of native BChE is the inherent inefficiency of the enzyme: \(k_{cat} = 0.07/s\) and \(K_m = 4.5\ \mu M\). It would require massive doses to detoxify cocaine in a human (Sun et al., 2002a). Guided by molecular modeling, two amino acid substitutions, Ala328Trp/Tyr332Ala, were introduced into wild-type BChE to allow better orientation of (−)-cocaine for enzymatic hydrolysis after it has bound to the enzyme active site. The recombinant enzyme, CocH, is also primarily tetrameric, and similar to wild-type BChE, is not rapidly degraded as are monomeric or dimeric enzymes and has a 40-fold increase in catalytic activity. CocH has a \(k_{cat} = 2.6/s\) and \(K_m = 18\ \mu M\). After CocH pretreatment, decreased cocaine concentrations were found in rat tissue, and increased locomotor activity induced by cocaine was abolished in mice (Sun et al., 2002a). Rats pretreated with CocH showed no major change in the concentration of BE generated, but EME concentration was 8-fold greater than controls (Sun et al., 2002b). When rats with cocaine-induced hypertension were treated with 3 mg/kg CocH after an average of 108 seconds after cocaine administration, they had rapid reversal of blood pressure abnormalities (Gao and Brimijoin, 2004). Development of additional mutants of CocH, such as A199S/S287G/A328W/Y332G and A199S/F227A/S287G/A328W/Y332G, has yielded catalytic efficiency with hundreds to thousands times that of native BChE (Zheng et al., 2008). Investigators have fused A199S/S287G/A328W/Y332G with albumin to provide a longer half-life. When given as pretreatment or as a rescue after administration of 100 mg/kg cocaine, albumin-CocH resulted in improved mortality and prevention or resolution of convulsions. When given after cocaine, brain cocaine concentrations in treated rats were 4-fold less compared with controls (Brimijoin et al., 2008).

A CocE found in Rhodococcus spp. catalyzes cocaine hydrolysis with a \(k_{cat} = 7.8/s\) and \(K_m = 0.64\ \mu M\). CocE is effective in preventing convulsions and mortality and rescues mice from convulsions when given after a lethal dose of cocaine (Ko et al., 2009). CocE (1 mg i.v.) given to rats 1 minute after cocaine administration produced a 10-fold rightward shift in the cocaine-toxicity dose-response curve. Notably, when CocE is administered to rats up to 6 minutes after cocaine, there is still a significantly reduced mortality rate (Cooper et al., 2006). However, an immune response was noted with repeated administrations of CocE, and as anti-CocE antibodies increased, the clinical response to treatment declined (Ko et al., 2009). Double mutant CocE (T172R/G173Q) given to rhesus monkeys 10 minutes after cocaine improved mean arterial pressure, heart rate, and locomotor activity, even as anti-double mutant CocE antibody titers increased in the animals after repeated administrations (Collins et al., 2011, 2012).

Effective enzymatic therapy for acute cocaine toxicity has the potential to be curative, although significant caveats to its administration will apply. More than 40% of patients who present to the emergency department with cocaine toxicity do so more than 1 hour after cocaine use (Gitter et al., 1991). More concerning is another analysis that shows patients suffering an acute myocardial infarction after cocaine use presented after more than 18 hours (Amin et al., 1990). It is unknown whether enzymatic therapy will be effective in these late presenters. Pharmacoeconomically, enzymatic therapy will be costly. Unless there is significant benefit of enzymatic treatment in terms of patient mortality, major adverse events, or reductions in hospital resource utilization compared with current clinical management, it will be difficult to justify the significant cost. Given these hurdles, it is difficult to imagine enzymatic therapy supplanting cooling and benzodiazepines in the treatment of cocaine toxic patients.

**Vaccine and Enzyme Combinations.** Vaccines that actively immunize against cocaine can result in innate production of anti-cocaine antibodies that yield immune-mediated degradation of the cocaine molecule. Although more suited to treat cocaine addiction by preventing the entry of cocaine into the CNS and the resultant reinforcing effects, it has also shown some promise in acute toxicity, reducing sequelae in mice and humans (Fox et al., 1996; Martell et al., 2009). Anti-cocaine antibody binding allows for rapid sequestration of the toxin in plasma. As discussed above, enzymatic degradation enhances elimination of active cocaine; in combination, it is believed that enzymatic treatment and prior vaccination work synergistically to prevent cocaine toxicity. Data show higher plasma cocaine and cocaine metabolite concentrations in mice treated with vaccine and CocH, suggesting endogenously produced antibodies trap cocaine in the plasma, possibly preventing entry into the CNS, and allow greater metabolism by CocH (Brimijoin et al., 2013). When the administration of cocaine vaccine [8100-1 KLH SNC vaccine (norcocaine hapten-conjugated keyhole limpet hemocyanin)] is compared with pretreatment with a quadruple mutant CocH (A199S/S287G/A328W/Y332G), each agent alone was not sufficient to prevent decreased grip strength or increased locomotor activity in cocaine-toxic mice (Carroll et al., 2012; Gao et al., 2013). Combination treatment of CocH and vaccine resulted in no loss of grip strength and greatly reduced locomotor activity (Carroll et al., 2012). Furthermore, this combination afforded almost total protection from alanine aminotransferase (ALT) elevation, suggesting that the liver cells were protected from injury when hepatotoxic doses (120 mg/kg i.p.) were administered (Gao et al., 2013). The protection from ALT elevation was equivalent to that when cocaine antibody was given, suggesting that the mice who received the vaccine went on to produce antibody and reaped the same benefit. Of note, cocaine-induced hepatotoxicity is specific to rodents and does not typically occur in humans. Mice treated with adeno-associated viral vector pAAVio-CASL-CocH C-W-SV40 encoding cDNA for C-terminally truncated CocH developed significant CocH activity and normal serum ALT after treatment with cocaine 120 mg/kg i.p. compared with mean ALT concentration of 18,000 units/ml in untreated subjects 3 months after vector administration (Gao et al., 2013). The use of an effective vaccine against cocaine has the potential to reduce toxicity substantially, although issues regarding bioethics and public health resource utilization must be considered.
Would this vaccine be offered broadly or to those who abuse and are psychologically addicted to cocaine? Could it become mandated in some cases, and what effects would that have on patient autonomy? Finally, there is the potential for riskier behavior; some may try to overcome the vaccine with higher doses whereas others may experiment with cocaine with the perception that there is an easy and effective treatment (Young et al., 2012). Significant more development of this modality and the evaluation of bioethical issues surrounding its use are required before this is a reasonable treatment option.

**Lipid Emulsion.** Use of an intravenous 20% lipid emulsion was initially described as a rescue therapy for toxicity to local anesthetics (Weinberg et al., 1998; Rosenblatt et al., 2006), although it has now shown benefit in refractory cases of various overdoses (Jamaty et al., 2010). Case reports describe the effective use of intravenous lipid emulsion bolus followed by infusion in patients with hemodynamic compromise secondary to cocaine toxicity (Jakkala-Saibaba et al., 2011; Arora et al., 2013). The precise mechanism of lipid emulsion in overdose is not fully elucidated. Theories including the formation of a “lipid sink” with sequestration of a lipophilic xenobiotic, such as cocaine, in the plasma, creating a gradient off the target organs and possibly enhancing elimination have been proposed (Weinberg et al., 1998). The partition coefficient (log D) and the volume of distribution are properties of chemicals found to be predictive of in vitro reductions of drug concentrations after lipid emulsion treatment. The more positive the log D and the greater the volume of distribution, the more likely a drug is to be highly lipid soluble and therefore more likely that lipid emulsion will be effective (French et al., 2011). The distribution constant (log D) correlates well with the log P and is a more precise estimate of lipid solubility because it takes pH into account (Samuels et al., 2012). Cocaine has a log D of 1.14 (Wilson et al., 2004) and volume of distribution of 1.96 l/kg (Chow et al., 1985), suggesting that lipid emulsion may be helpful in cases refractory to conventional management. Additionally, lipid emulsion is a component common in parenteral feeding preparations, is already present in many hospitals, and its cost is almost negligible relative to innovative pharmaceuticals. Although it has been used clinically, the paucity of evidence precludes lipid emulsion from being considered a conventional therapy, although its use is far more available to the clinician at the bedside. Lipid emulsion treatment of toxic exposures is in its infancy, and there remain significant questions regarding its efficacy and potential harm. Concerns include impairment of therapeutic medications via the same mechanism as inactivation of the toxin [log D for diazepam and midazolam is 3.86 and 3.68, respectively (Wilson et al., 2004)], induction of pancreatitis, and interference with the laboratory analysis of serum constituents such as lactate. Lipid emulsion remains an investigational final treatment option available to providers when patients are acutely decompensating.

**Conclusion**

The perfect cocaine antidote must be easily deliverable to a patient manifesting signs and symptoms of severe cocaine toxicity, namely cerebral, coronary, or peripheral vasoconstriction, or life-threatening hyperthermia. This substance would rapidly halt the actions of cocaine centrally by neutralizing cocaine in the plasma before it has traversed the blood-brain barrier, traversing the barrier itself, or creating a diffusion gradient to pull cocaine from the CNS into the plasma. This substance should perform better than symptomatic treatments to such a great degree that this product would be economically viable against generic benzodiazepines. This ideal has proven elusive though because of the complexity of cocaine’s pathophysiologic effects.

The preponderance of preclinical studies evaluating antidotal therapies for cocaine are elegant experiments that help further elucidate cocaine’s actions at receptors and the ability of enzymes to catalyze its hydrolysis. The majority are proof of concept studies that pretreat subjects with the investigational agent before administration of cocaine. Excitement for a potential contender is enhanced by the studies that show clinical improvement with a delay of several minutes between cocaine and antidote administration. Currently, 10 minutes is the longest delay to treatment with retained benefit. Several potentially harmful active metabolites of cocaine, such as norcocaine and BE, may be present in greater concentrations relative to cocaine by the time a patient develops symptoms, presents to an emergency department, and is treated. The efficacy of experimental treatments on these metabolites or when given after a delay between cocaine administration and treatment is unknown. With regards to non-human-derived proteins, antibody formation and the resultant immune response will have to be considered because an acutely cocaine-toxic patient may be extremely susceptible to significant immune-mediated reactions. This is not likely an issue the first time a patient is treated, but the addictive nature of the drug suggests that patients may require treatment several times. These patients are also those from whom an accurate history of prior treatments would be very difficult to obtain. Other modalities such as antipsychotics predispose to anticholinergic effects that are potentially additive to the most severe risks of cocaine toxicity, namely hyperthermia, arrhythmia, and seizures. The last issue in the development of new pharmaceuticals is their potentially exorbitant cost, especially for enzymes or other complex proteins. Any new antidotal therapy would have to be far more efficacious than generic benzodiazepines and phentolamine to be a cost-effective care strategy. Given these cost issues, clinical studies proving efficacy will need to be powered to show superiority to current treatment modalities, which will require more patients than studies performed to show noninferiority. Cocaine toxicity remains a significant cause of death and permanent disability. Cooling, high dose, rapid-acting benzodiazepines, and adrenergic antagonists are the foundation of current clinical management. Lipid emulsion has been effective in managing refractory cases and may be an economical rescue treatment of patients with severe cocaine toxicity. Experimental agents hold promise, although there are many issues to contend with before these are available at the bedside. These agents must not predispose the patient to arrhythmia or interfere with normal neurotransmitter function. They also need to be effective after a significant delay between cocaine exposure and presentation. Immunogenicity must be minimal, as such critically ill patients would fare poorly with additional anaphylactoid or anaphylactic reactions. Even considering the significant and numerous hurdles, the ideal agent may be on the horizon and for that we can wait and hope. For now, years of treating cocaine toxicity have supported the
safe and effective use of cooling and benzodiazepines in these critically ill patients.

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