Cocaine Toxicity in the Intensive Care Unit

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KEY POINTS

- Cocaine toxicity represents a multi-organ syndrome, comprising both acute toxicity and chronic complications.
- Cocaine-related presentations requiring intensive care admission suffer the greatest mortality and morbidity.
- Cocaine toxicity can present as an acute central nervous system, respiratory, cardiac, vascular, renal, or psychiatric crisis.
- While supportive management is the general rule, some cocaine-related crises require specific therapies.

INTRODUCTION

Cocaine blocks the reuptake of catecholamines and dopamine within the synaptic cleft, resulting in accumulation and overstimulation of the postsynaptic nerve.[1] It also antagonises sodium channels, resulting in impaired nerve conduction. It prolongs depolarization and decreases the amplitude of action potential within the cardiac myocyte, resulting in malignant arrhythmias.[1,2] It has both immunosuppressive and proinflammatory actions and is a potent prothrombotic agent.

Clinical signs of acute toxicity include palpitations, epistaxis, sweating, headache, anxiety, tremors, muscle spasm, and hyperventilation.[3] Acute cocaine exposure at higher doses results in hyperthermia, hypertension, tachycardia, mydriasis, seizures, stupor, and cardiac and respiratory depression. Progression to death within 2 to 3 minutes has been described.[1] Mortality is high in those requiring admission to intensive care, with one Irish study showing cocaine-related admission mortality to be 52.6%.[4]

The treatment of acute cocaine toxicity is largely supportive, with the goals of resolving sodium-channel blockade, catecholamine-mediated effects, and agitation. The following is a summary of the clinical features and management strategies for cocaine toxicity.

CARDIAC TOXICITY

Common manifestations of cardiac toxicity include coronary and systemic vasoconstriction, arrhythmias, contraction band necrosis, accelerated atherosclerosis, dilated cardiomyopathy, and acute myocardial infarction.[5,6] Cocaine abusers have a 5-fold increase in myocarditis compared with nonusers.[7]

It is reported that approximately 5% to 10% of all emergency department visits in the United States are associated with cocaine toxicity.[2,6,8] Chest pain is the most common presentation in this population. Cocaine-related chest pain admissions cost approximately $83 million annually in the United States.[2]

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TAKE ONLINE TEST

Acute ingestion is associated with ischemic cardiac events. Increased oxygen demand from systemic hypertension, tachycardia, and increased inotropy, coupled with coronary vasospasm, results in ischemic injury. Direct coronary endothelial injury and resulting thrombosis exacerbates this ischemia.[1]

Chronic cocaine ingestion accelerates atheromatous disease, with 40% of young abusers having coronary artery disease on autopsy following fatal myocardial infarction. Up to 50% of chronic abusers show signs of left ventricular hypertrophy and dilated cardiomyopathy, with decreased left ventricular ejection fraction.[1,5]

Acute myocardial infarction can present weeks after last use and with normal coronary arteries on coronary catheterization.[5]

Intensive Care Unit Management of Cocaine-Related Cardiac Toxicity

Management of cardiac toxicity is symptom based. General therapy principles are to reduce both catecholaminergic effects (hypertension, tachycardia, vasospasm) and sodium-channel blockade. Sedation with benzodiazepines remains the cornerstone of treatment but whilst this can effectively treat agitation, this approach may not completely resolve the tachycardia, hypertension, and vasospasm of acute toxicity.[9]

The use of β-blockers has long been contraindicated, due to concerns regarding *unopposed α-adrenergic stimulation*. These concerns permeate teaching but remain controversial in view of agents with both αand βantagonist activity, variable receptor selectivity based on the dose and route of antagonist used, and the different time-course and degree of toxicity in any given case.[9] In a recent review, no adverse outcomes were reported after combination of αand βblockers (eg, labetalol and carvedilol) administered to 1744 patients with mild to severe cocaine toxicity. These agents have been recommended for treatment specifically of hypertension and tachycardia in acute toxicity.[9]

Calcium-channel antagonists may decrease vasospasm and hypertension, but not necessarily tachycardia. Nitroglycerin is not recommended as therapy as it is associated with severe hypotension and reflex tachycardia. Specific antagonism at α-1 receptors (eg, with phentolamine) has limited evidence but may improve hypertension, myocardial ischemia, and vasospasm.[9]

Wide-complex tachyarrhythmias can be treated with lidocaine, notwithstanding theoretical concerns regarding its sodium-channel blocking effects. It is believed that competitive inhibition displaces cocaine from the channel, allowing its reactivation after the lidocaine molecule quickly dissociates.[10] Recommendations include a bolus of lidocaine (1-1.5 mg/kg intravenously, repeated every 5 minutes as needed to a maximum of 300 mg), followed by an infusion of 1 to 4 mg/min.[10] Clinically decompensated patients, those with hypotension, diaphoresis, and psychomotor agitation, require supportive management and sedation (see sections below) and consideration of sodium bicarbonate therapy analogous to the management of tricyclic antidepressant toxicity.[10] A bicarbonate bolus of 1 to 2 MEq/kg, with titration to QRS $<$ 110 ms is recommended.[10,11] Should the serum pH approach 7.55, alternate treatments should be considered. Unlike tricyclic antidepressant toxicity, in acute cocaine tachyarrhythmia there is no recommendation to use of hypertonic saline.[10] Remaining advanced cardiac life support tenets are unchanged.[11]

Management of cocaine-associated myocardial infarction mirrors that of non–cocaine-associated infarction with subtle differences. Early administration of benzodiazepines to relieve catecholaminergic surge is recommended (Grade 1/B) and intravenous phentolamine for persistent hypertension and chest pain is recommended as an alternative to nitroglycerin (Grade IIb/C).[12] Otherwise, evaluation by electrocardiogram and troponin levels, and stabilization by early revascularization is unchanged. Consideration of cocaine use as etiology of myocardial ischemia should be made in young patients, wherein chronic cocaine abuse accelerates atherosclerotic disease.

CENTRAL NERVOUS SYSTEM TOXICITY

Classic presentations of acute cocaine toxicity include intracerebral and subarachnoid hemorrhage, cerebral vasculitis, optic neuropathy, stroke, seizures, and agitation.[3,13,14] Chronic abuse is associated with cerebral atrophy.

Stroke may occur due to ischemic vasospasm, cerebral artery thrombosis, cerebral vasculitis, and acute hemorrhage.

Seizures result from central nervous system activation. Repetitive small doses of cocaine result in a focus of epileptiform activity, a phenomenon known as *kindling*. The incidence of seizures in active cocaine users is 10.3%.[1,14]

Excited delirium presents as profound psychomotor agitation and delirium. Late-stage excited delirium is associated with high mortality given a profound hyperthermia, metabolic acidosis, and catecholamine surge that predisposes to fatal cardiac arrhythmia.[15]

Intensive Care Unit Management of Cocaine-Related Central Nervous System Toxicity

Treatment of cocaine-related central nervous system toxicity is supportive and involves intensive care unit (ICU) standard management for the clinical presentation that is being manifested.

Agitation and excited delirium are managed with benzodiazepines; large doses may be required.[9] The α-2-receptor agonist dexmedetomidine may also be considered.[9] Ketamine has been shown to be effective in the control of excited delirium in the

prehospital setting and has been suggested as an alternative agent for mildly agitated patients in the emergency department. It should be avoided in late-stage excited delirium, typified by hyperthermia and metabolic acidosis.[15]

RESPIRATORY TOXICITY

Pulmonary complications range from asthma to fatal pulmonary hemorrhage.[1,16]

Lower airway manifestations result from direct irritant effects with resulting bronchoconstriction and noncardiogenic pulmonary edema.[17] There are case reports of cocaine-associated bronchiolitis obliterans.[18] Cocaine additives like talc, silica, or cellulose result in inflammatory granulomas and a pneumoconiosis-like reaction.[19]

Hypersensitivity pneumonitis, or *crack lung*, results from thermal injury after inhalation of volatilized cocaine ($> 700°C$), a hypersensitivity reaction to nonvolatilized impurities and adrenergic receptor stimulation resulting in macrophage activation, basal cell hyperplasia, ciliary dysfunction, and profound local vasoconstriction.[20] This syndrome manifests within 48 hours of ingestion as fever, dyspnea, wheeze, and productive cough with hemoptysis. Chest radiography shows diffuse interstitial and alveolar infiltrates, interlobular septal thickening, peribronchial nodules, and ground-glass opacities.[1,20,21]

Alveolar hemorrhage results from bronchial and pulmonary vasoconstriction resulting in hemoptysis.[1] Rarely, pulmonary infarction results from a combination of severe vasoconstriction and prothrombotic effects.

Chronic cocaine abuse may cause pulmonary hypertension and right heart failure as a result of medial hypertrophy of the pulmonary arteries, pulmonary hemorrhage, and intense vasospasm in acute toxicity.[1,22]

The method of ingestion can contribute to pulmonary complications. Valsalva following inhalation has been linked to development of pneumothorax, pneumomediastinum, and pneumopericardium.[1]

ICU Management of Cocaine-Related Respiratory Toxicity

Patients with pneumomediastinum and pneumothorax should be closely monitored for decompensation.[1]

Consider high-dose steroids for eosinophilic pneumonia. Anticipate resolution of chest radiography over weeks to months.[20]

Management of cocaine hypersensitivity pneumonitis is supportive, including drug cessation, oxygen supplementation, and bronchodilators, with expected radiographical resolution in 3 to 14 days. Hypersensitivity pneumonitis may be associated with physical exam features of bilateral burnt thumbs and corneal ulcers, which may be of use in the undifferentiated hypoxic patient.[20,21]

Development of pulmonary hypertension requires investigation into etiology. If proven to be due to cocaine use, specific therapy for pulmonary arterial hypertension is required.[23]

OTOLARYNGOLOGICAL TOXICITY

Upper airway complications are common in cocaine snorters; these include epistaxis, septal perforations, and nasal and oral mucosal ulcerations resulting from pathologic vasoconstriction. Local complications include preseptal cellulitis, palatal necrosis, and osteolytic sinusitis.[1,24]

Facial and mucosal thermal burns and resulting scarring result from inhalation of heated vapors and accidental ignition of freebase cocaine during smoking.[1]

ICU Management of Cocaine-Related Otolaryngological Toxicity

The management of cocaine-related otolaryngological injury is mainly supportive. Close monitoring for possible airway compromise in the setting of chemical or thermal injury is prudent. Additional attention is required to rule out injuries to other facial structures (eg, conjunctiva, skin).

GASTROINTESTINAL TOXICITY

Mesenteric and gastric vasoconstriction result in acute ischemic injury, ulceration, and perforation.[25]

Cocaine abuse is associated with both acute and chronic liver toxicity. Toxicity ranges from elevation of liver enzyme levels in chronic users to fulminant liver failure.[6]

Complications of drug trafficking are also common. It is important to distinguish between *stuffers* and *packers*. Stuffers hastily swallow or place a small amount of drug within a body orifice, often to evade impromptu police interaction. Given the hastiness

of concealment these packages often leak, but the total dose may only represent a few recreational doses. Conversely, packers conceal large quantities of high-purity drugs in secure packaging in a premeditated effort to smuggle contraband. Cocaine packers arriving at an airport might have ingested 1 kg of cocaine in 100 small packets, any one of which contains a lethal dose. Package leak results in severe toxicity. Mechanical bowel obstruction can also occur in this setting. Further, slow leaks can cause large ulcerations secondary to intense local vasoconstriction.[1,26,27]

ICU Management of Cocaine-Related Gastrointestinal Toxicity

Cocaine-related ischemic colitis is treated supportively. Institute bowel rest and empiric antibiotics.[1,28] Indications for surgical management are similar to other presentations of acute abdomen.

Body stuffers can be managed expectantly if asymptomatic or minimally symptomatic. Efforts to retrieve the stuffed drugs are rarely warranted, unless easily accessible (eg, in the rectal vault or vagina).[27,29,30]

Body packers can be managed according to the modified Hillingdon Hospital protocol[27] or other similar algorithms.[26,31]

VASCULAR TOXICITY

Endothelial injury, vasospasm, and thrombosis result in small- and large-vessel occlusion and ischemic injury.[1,32]

Large-vessel thrombosis is described, including the aorta. Typically, this is a complication of acute ingestion, manifesting within 12 hours of ingestion.[6,13,33]

Levimasole, a cocaine contaminant, is present in up to 69% of cocaine apprehended by US law enforcement officials. Exposure to this contaminant over time causes profound agranulocytosis, an ANCA(antineutrophil cytoplasmic antibody)-associated vasculitis with constitutional symptoms, and cutaneous necrotizing vasculitis, especially of the nose and ears.[34,35]

ICU Management of Cocaine-Related Vascular Toxicity

The management of cocaine-related vascular toxicity is mainly supportive. This may include reverse isolation for infection mitigation and colony-stimulating factors for agranulocytosis. A systematic approach is required to rule out other etiologies for vasculitis.[36]

RENAL TOXICITY

Cocaine-associated rhabdomyolysis is associated with renal failure in 30% of cases and is the most common mechanism of acute kidney injury in cocaine abusers.[1,35] Other described etiologies of renal damage include direct ischemic injury resulting from local vasoconstriction, renal endothelium damage, renal artery arteriosclerosis, oxidative stress, glomerular matrix synthesis alteration, and thrombosis.[35]

ICU Management of Cocaine-Related Renal Toxicity

The management of cocaine-related renal injury is mainly supportive, with monitoring for the need for renal replacement therapy.

See *Trauma Management*, below, for management of cocaine-related rhabdomyolysis.

TRAUMA MANAGEMENT

Cocaine-related trauma carries risks of delayed gastric emptying with increased risk of aspiration during intubation.[1]

Cocaine-related trauma should be approached with caution. Be wary of falsely normalized blood pressure in hemorrhagic shock, which masks severity of blood loss.[1]

Cocaine-associated rhabdomyolysis often results from seizures, decreased levels of consciousness resulting in prolonged muscle compression, or direct skeletal muscle vasoconstriction and ischemic injury. Cocaine-related muscle injury can result in more abrupt increase in compartment pressure than if caused from external blunt trauma.[1] Cocaine-related rhabdomyolysis is treated with generous fluid resuscitation, electrolyte management, and consideration of hemodialysis, analogous to management of non–cocaine-associated rhabdomyolysis. Management of cocaine-associated compartment syndrome is analogous to typical compartment syndrome with close monitoring and consideration of fasciotomy.[1]

Extra caution should be applied to the chronic abuser with abrupt cessation (admission after emergency surgery or trauma) as withdrawal manifestations are pronounced. Withdrawal should be managed supportively.

PSYCHIATRIC AND MISCELLANEOUS TOXICITY

Comorbid psychiatric disorders are common in cocaine abusers, with 70% suffering from one or more of mood disorders, attention deficit, panic attacks, paranoid ideation, and behaviour conducive to violence. Agitated delirium accounts for 10% of cocaine-related deaths.[1]

Hyperthermia as high as 45.6°C rectally is reported. Hyperthermia serves as a marker of severe toxicity and is more common when ambient temperatures are high. It is associated with death, renal failure, disseminated intravascular coagulation, acidosis, hepatic injury, and rhabdomyolysis.[7]

ICU Management of Cocaine-Related Psychiatric and Miscellaneous Toxicity

Cocaine abusers have increased susceptibility to posttraumatic stress following traumatic injury.[1]

Effective treatment for hyperthermia involves potent sedation and aggressive cooling; ice-water immersion is described.[37]

Case reports describe confusion from cocaine-related stroke being misinterpreted as sepsis, and cocaine-related movement disorders being misinterpreted as drug reactions or electrolyte abnormalities.[1]

SUMMARY

Cocaine toxicity has a myriad of end-organ complications, both in acute ingestion and chronic abuse. An appreciation for nuances of this presentation is required to provide excellent critical care. Treatment is largely supportive, but rapid control of agitation as well as recognition and treatment of both acute and chronic effects is required to mitigate the poor outcomes in this vulnerable patient population.

REFERENCES

1. Shanti CM, Lucas CE. Cocaine and the critical care challenge. *Crit Care Med*. 2003;31(6):1851-1859. doi:10.1097/01.CCM.0000063258.68159.71
2. Maraj S, Figueredo VM, Morris ; D Lynn. Cocaine and the Heart. *Clin Cardiol*. 2010;5:264-269. doi:10.1002/clc.20746
3. Pereira RB, Andrade PB, Valentão P. A Comprehensive View of the Neurotoxicity Mechanisms of Cocaine and Ethanol. *Neurotox Res*. 2015;28(3):253-267. doi:10.1007/s12640-015-9536-x
4. Galvin S, Campbell M, Marsh B, O'Brien B. Cocaine-related admissions to an intensive care unit: a five-year study of incidence and outcomes. *Anaesthesia*. 2010;65(2):163-166. doi:10.1111/j.1365-2044.2009.06189.x
5. Graziani M, Sarti P, Arese M, Magnifico MC, Badiani A, Saso L. Cardiovascular Mitochondrial Dysfunction Induced by Cocaine: Biomarkers and Possible Beneficial Effects of Modulators of Oxidative Stress. *Oxid Med Cell Longev*. 2017;2017:1-15. doi:10.1155/2017/3034245
6. Graziani M, Antonilli L, Togna AR, Grassi MC, Badiani A, Saso L. Cardiovascular and Hepatic Toxicity of Cocaine: Potential Beneficial Effects of Modulators of Oxidative Stress. *Oxid Med Cell Longev*. 2016;2016:1-14. doi:10.1155/2016/8408479
7. Keskin M, Hayıroğlu MI, Keskin Ü, et al. The most dangerous complication of intranasal cocaine abuse in a young man: cardiac arrest. *Am J Emerg Med*. 2016;34(8):1731.e5-7. doi:10.1016/j.ajem.2015.12.043
8. Hollander JE, Hoffman RS, Gennis P, et al. *SCIENTIFIC ADVANCES Prospective Multicenter Evaluation of Cocaine-Associated Chest Pain*.; 1994. https://onlinelibrary-wiley-com.proxy.queensu.ca/doi/pdf/10.1111/j.1553-2712.1994.tb02639.x. Accessed October 19, 2018.
9. Richards JR, Garber D, Laurin EG, et al. Treatment of cocaine cardiovascular toxicity: a systematic review. *Clin Toxicol*. 2016;54(5):345-364. doi:10.3109/15563650.2016.1142090
10. Hoffman RS. Treatment of patients with cocaine-induced arrhythmias: bringing the bench to the bedside. *Br J Clin Pharmacol*. 2010;69(5):448-457. doi:10.1111/J.1365-2125.2010.03632.X@10.1111/(ISSN)1365-2125.CARDIOLOGYNOV10
11. Lavonas EL, Drennan IR, Gabrielli A, et al. Part 10: Special Circumstances of Resuscitation. 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. 2015. doi:10.1161/CIR.0000000000000264
12. Mccord J, Jneid H, Hollander JE, et al. Management of Cocaine-Associated Chest Pain and Myocardial Infarction A Scientific Statement From the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology AHA Scientific Statement. 2008. doi:10.1161/CIRCULATIONAHA.107.188950

13. Farrell CM, Cucu F. Cocaine-Related Acute Spinal Cord Infarction. *R I Med J*. 2013;101(1):28-29. http://www.medscape.com/. Accessed October 19, 2018.
14. Sordo L, Indave BI, Degenhardt L, et al. A systematic review of evidence on the association between cocaine use and seizures. *Drug Alcohol Depend*. 2013;133(3):795-804. doi:10.1016/j.drugalcdep.2013.08.019
15. Ho JD, Smith SW, Nystrom PC, et al. Successful Management of Excited Delirium Syndrome with Prehospital Ketamine: Two Case Examples. *Prehospital Emerg Care*. 2013;17(2):274-279. doi:10.3109/10903127.2012.729129
16. Cruz R, Davis M, Tamarin F, Brandstetter RD, Karetzky M, Rochelle N. Pulmonary manifestations of inhaled street drugs. *Hear Lung*. 1998;27(5):297-305. https://ac.els-cdn.com/S0147956398900498/1-s2.0-S0147956398900498-main.pdf?_tid=245d1ca2-c444-48e7-ac5f-b89bbb970534&acdnat=1539957110_f8fc8cf6af7a2639b26b309d81b9c55c. Accessed October 19, 2018.
17. Tashkin DP, Kleerup EC, Koyal SN, Marques JA, Goldman MD. Acute Effects of Inhaled and IV Cocaine on Airway Dynamics. *Chest*. 1996;110(4):904-910. doi:10.1378/chest.110.4.904
18. Patel RC, Dutta D, Schonfeld SA. Free-base cocaine use associated with bronchiolitis obliterans organizing pneumonia. *Ann Intern Med*. 1987;107(2):186-187. doi:10.7326/0003-4819-107-2-186
19. Albertson TE, Walby WF, Derlet RW. Stimulant-induced pulmonary toxicity. *Chest*. 1995;108(4):1140-1150. http://go.galegroup.com.proxy.queensu.ca/ps/anonymous?id=GALE%7CA17467998&sid=googleScholar&v=2.1&it=r&linkaccess=abs&issn=00123692&p=AONE&sw=w. Accessed October 19, 2018.
20. Mégarbane B, Chevillard L. The large spectrum of pulmonary complications following illicit drug use: Features and mechanisms q. *Chem Biol Interact*. 2013;206:444-451. doi:10.1016/j.cbi.2013.10.011
21. Bulbena-Cabre A, Dunn NR, Swift RG. "Crack Lung." *J Addict Med*. 2015;9(2):164-165. doi:10.1097/ADM.0000000000000102
22. Akwe JA. Pulmonary Effects of Cocaine Use. *J Lung, Pulm Respir Res*. 2017;4(2):00121. doi:10.15406/jlprr.2017.04.00121
23. Simonneau G, Robbins IM, Beghetti M, et al. Updated Clinical Classification of Pulmonary Hypertension. *J Am Coll Cardiol*. 2009;54:S43-S54. doi:10.1016/j.jacc.2009.04.012
24. Cury PR, Oliveira MGA, dos Santos JN. Periodontal status in crack and cocaine addicted men: a cross-sectional study. *Environ Sci Pollut Res*. 2017;24(4):3423-3429. doi:10.1007/s11356-016-7918-0
25. Boghdadi MS, Henning RJ. Cocaine: Pathophysiology and clinical toxicology. *Hear Lung*. 1997;26(6):466-483. doi:10.1016/S0147-9563(97)90040-6
26. Hoffman RS, Smilkstein MJ, Goldfrank LR. Whole bowel irrigation and the cocaine body-packer: A new approach to a common problem. *Am J Emerg Med*. 1990;8(6):523-527. doi:10.1016/0735-6757(90)90155-S
27. Alfa-Wali M, Atinga A, Tanham M, Iqbal Q, Meng A-Y, Mohsen Y. Assessment of the management outcomes of body packers. *ANZ J Surg*. 2016;86(10):821-825. doi:10.1111/ans.13226
28. Miller J, Hendren S, Liscum K. Giant gastric ulcer in a body packer. *J Trauma*. 1998;(45):617-619.
29. Piero Covarelli P, Burini G, Castellani E, et al. Surgical treatment in drug body packers. *Am Surg*. 2014;1(80):E76.
30. Cregler LL, Mark H. Medical Complications of Cocaine Abuse. *N Engl J Med*. 1986;315(23):1495-1500. doi:10.1056/NEJM198612043152327
31. Kolodgie FD, Virmani R, Cornhill JF, Herderick EE, Smialek J. Increase in atherosclerosis and adventitial mast cells in cocaine abusers: An alternative mechanism of cocaine-associated coronary vasospasm and thrombosis. *J Am Coll Cardiol*. 1991;17(7):1553-1560. doi:10.1016/0735-1097(91)90646-Q
32. Chang RA, Rossi NF. Intermittent Cocaine Use Associated With Recurrent Dissection of the Thoracic and Abdominal Aorta. *Chest*. 1995;108(6):1758-1762. doi:10.1378/chest.108.6.1758
33. Larocque A, Hoffman RS. Levamisole in cocaine: Unexpected news from an old acquaintance. *Clin Toxicol*. 2012;50(4):231-241. doi:10.3109/15563650.2012.665455
34. Pendergraft WF, Herlitz LC, Thornley-Brown D, Rosner M, Niles JL. Nephrotoxic Effects of Common and Emerging Drugs of Abuse. *Clin J Am Soc Nephrol*. 2014;9(11):1996-2005. doi:10.2215/CJN.00360114
35. Lee KC, Ladizinski B, Federman DG. Complications Associated With Use of Levamisole-Contaminated Cocaine: An Emerging Public Health Challenge. *Mayo Clin Proc*. 2012;87(6):581-586. doi:10.1016/j.mayocp.2012.03.010
36. Laskowski LK, Landry A, Vassallo SU, Hoffman RS. Ice water submersion for rapid cooling in severe drug-induced hyperthermia. *Clin Toxicol*. 2015;53(3):181-184. doi:10.3109/15563650.2015.1009994