Assessment and Management of Toxidromes in the Critical Care Unit

J.J. Rasimas, MD, PhD, FAPM[a,*], Courtney M. Sinclair, BA[b]

KEYWORDS

• Toxidrome • Delirium • Antidote • Physostigmine • Flumazenil • Naloxone
• Psychosomatic

KEY POINTS

- In cases of suspected toxidrome exposure, whether it be purposeful, accidental, or iatrogenic, toxidromic presentation that is consistent with the history and physical examination should guide the judicious use of antidotes.
- Although surveys of available agents in the environment (e.g., home, hospital ward) can be useful aids to the diagnostic process, the patient's vital signs and physical examination are the best guides to medical intervention.
- The focus of treatment always should be the patient and the patient's symptoms, not the toxin or the assays that may or may not identify it.
- Good supportive care with prioritized attention to emergent physiologic needs is the cornerstone of management; detailed assessment and reassessment with synthesis of data over time is essential to this process.
- Pharmacologic interventions should be targeted to underlying toxic pathophysiology whenever possible with attention to not exacerbating delirium and minimizing its severity and duration.

INTRODUCTION

Psychiatrists must be concerned about toxic states, primarily because poisoned patients often have made choices that led to the exposure and its consequences, and those choices have mental health determinants and implications. But consulting psychiatrists may play a broader role in the critical care management of patients affected

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[a] Consultation - Liaison Psychiatry, Hennepin County Medical Center, University of Minnesota, 701 Park Avenue, R7.255, Minneapolis, MN 55415, USA; [b] Veterinary and Biomedical Sciences, University of Minnesota, 1988 Fitch Avenue, Saint Paul, MN 55108, USA
* Corresponding author.
E-mail address: joseph.rasimas@hcmed.org

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by medications and other substances that goes far beyond psychiatric assessment and disposition planning after recovery from overdose. Toxic delirium abounds in the intensive care unit (ICU), where care interventions have as much or more to do with patients' neuropsychological functioning and experiences there as the critical illnesses they suffer.[1,2] Although psychiatric education offers some expertise in clinical pharmacology to inform differential diagnostic considerations of medication and substance toxicity, formal medical toxicology training for psychiatrists is rare.[3]

The most important diagnostic factor in uncovering a toxic etiology is the clinician's openness to the possibility of its existence. Therefore, a consulting psychiatrist, already prepared to perform the detail-oriented work of sorting out behavioral manifestations of disease, can be a vital asset at the bedside if also attuned to the role of purposeful, accidental, and iatrogenic exposures in the ICU. This article summarizes the presentation, evaluation, and treatment of toxidromes relevant to the work of acute psychosomatic medicine.

GENERAL APPROACH

Because the brain is the organ most commonly affected by acute poisoning, any patient whose behavior, level of consciousness, or established neuropsychiatric baseline are disturbed should prompt concerns about toxicity.[4] From the standpoint of central nervous system (CNS) function and diagnosis by the *Diagnostic and Statistical Manual of Mental Disorders*, the presence of delirium is therefore a major reason to suspect a toxic etiology. It is not only the symptomatic management of delirial states that defines much of consultation-liaison (C-L) psychiatry in the hospital setting, but also the medical detective work necessary to ascertain the possible causes of the syndrome.

Often, substance-related toxicity is not considered because of patients' purposeful deception or impairments in communication due to age, language barriers, underlying CNS ailment, or manifestations of the toxic exposure, itself. Physicians also are disinclined to look toward their own interventions as a primary cause for harm, thus further diminishing their attunement to toxic states induced by iatrogeny. Even in medical inpatients with many comorbid conditions that can affect brain function, adverse effects of the drugs used to treat those illnesses are likely to be the most common cause of delirium.[5] Toxicity from medications or other substances should be considered in patients who acutely develop seizures, coma, respiratory distress, shock, arrhythmias, metabolic acidosis, severe vomiting and diarrhea, or other puzzling multisystem disorders without known etiology.[6] The possibility even needs to be considered of substances being brought into the hospital and ingested by patients after an episode of care has commenced.

A detailed review of the history and medical record is essential to make sense of the time-course of evolution of a toxic or withdrawal state. Special attention should be paid to the first set of vital signs and physical examination documented, ideally before any medical interventions have been performed that would alter the phenomenology of the presenting problem. Data from emergency medical personnel can be particularly informative. The timing of significant changes in autonomic status, peripheral reflexes, behavior, and cognition also should be noted, with reference to medications given. Then, any subsequent shifts in patterns of autonomic indices and behavior during the hospital course should open the possibility of a new toxic process mediated by either the treatment process itself or withdrawal from discontinued substances.

Certain constellations of signs and symptoms, commonly called toxidromes, may suggest poisoning by a specific class of compounds (**Table 1**). The findings represent direct physiologic manifestations of the pharmacology of the agents in question, thus providing objective clinical data about the status of the patient and what has been

Table 1
Toxidromes

Drug Class (Examples)	Clinical Manifestations
Anticholinergics (atropine, antihistamines, scopolamine, antispasmodics, tricyclic antidepressants, phenothiazines, antiparkinsonian agents, Jimson weed, psychedelic mushrooms)	Agitation, hallucinations, abnormal movements (eg, carphology), tachycardia, mydriasis, dry membranes, hyperthermia, decreased bowel sounds, urinary retention, flushed/dry skin
Cholinergics (organophosphates, carbamate insecticides, cholinesterase inhibitors)	Hypersalivation, lacrimation, urinary/fecal incontinence, gastrointestinal cramping, emesis (SLUDGE), bradycardia, diaphoresis, miosis, pulmonary edema, weakness, paralysis, muscle fasciculations
Opioids (oxycodone, hydrocodone, hydromorphone, fentanyl, morphine, propoxyphene, codeine, heroin)	Central nervous system (CNS) depression, respiratory compromise, miosis, bradycardia, hypotension, hypothermia, pulmonary edema, hyporeflexia, seizures
Sedative/Hypnotics (benzodiazepines, nonbenzodiazepine GABA agonists, barbiturates, ethanol, chloral hydrate, ethchlorvynol, meprobamate)	CNS depression, hyporeflexia, slow respirations, hypothermia, hypotension, and bradycardia (mild)
Sympathomimetics (psychostimulants, amphetamines, pseudoephedrine, phenylephrine, ephedrine, cocaine)	Hypertension, tachycardia, arrhythmias, agitation, paranoia, hallucinations, mydriasis, nausea, vomiting, abdominal pain, piloerection
Neuroleptics (chlorpromazine, promethazine, prochlorperazine, fluphenazine, perphenazine, haloperidol, olanzapine, quetiapine)	Hypotension, arrhythmias, oculogyric crisis, trismus, dystonia, ataxia, parkinsonism, neuroleptic malignant syndrome, anticholinergic manifestations (some)
Serotonergics (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, buspirone, tramadol, fentanyl, synthetic stimulants, dextromethorphan)	Akathisia, tremor, agitation, hyperthermia, hypertension, diaphoresis, hyperreflexia, clonus, lower extremity muscular hypertonicity, diarrhea

ingested. Recognition of such patterns can be informative, but clinical pictures are not always so obvious. Polydrug overdoses may result in overlapping and confusing mixed syndromes. Pharmacokinetic drug compartmentalization also is a factor, with peripheral manifestations not always matching up with those reflecting toxicity in the CNS. Nevertheless, recognizing the dominant features of particular classes of pharmacologic toxicities can be a vital diagnostic and therapeutic starting point to psychosomatic consultation in the ICU.

TOXIDROMES

The toxic syndromes most frequently encountered in the emergency and ICU setting are detailed in the following sections. The causes vary, with anticholinergic toxicity, sedative toxicity, and serotonin syndrome being common after suicidal overdose, cholinergic and opioid toxicity often being accidental or secondary to a recreational drug misadventure, and almost any syndrome potentially resulting from iatrogenic interventions. The most commonly used antidotes for these conditions, and for other toxic states not discussed in detail, are provided as a reference for the ICU psychiatrist in **Table 2**. Their specific indications are discussed under each toxidrome subsection below.

Table 2
Emergency antidotes

Toxin	Antidote	Dosing
Acetaminophen	*N*-acetylcysteine (NAC)	IV *or* PO/NG: 140 mg/kg over 1 h, then 70 mg/kg over 1 h q4h × 5 doses; then reassess toxin clearance, PT/INR, and transaminases.[a]
Anesthetics (local) and some cardiotoxins	Lipid emulsion	IV: 1 mL/kg bolus of a 20% solution followed by 0.25 mL/kg per min infusion to maintain cardiovascular stability.[b]
Anticholinergics	Physostigmine	IV: 2 mg over 4 min in adolescents and adults, may repeat q1-2h prn; 20 μg/kg (1 mg maximum) in children, may repeat q1-2h prn.
Benzodiazepines and non-benzodiazepine hypnotics	Flumazenil	IV: 0.5 mg over 30 s in adults, Consider lower doses in children; may use 0.005–0.01 mg/kg at 0.2 mg/min rate in children; may repeat q30–60 min prn.
β-Adrenergic blockers	Glucagon[c]	IV: 50 μg/kg over 1–2 min up to 10 mg maximum followed by hourly infusion of half to full initial dose.
Calcium channel blockers	Calcium	IV: 1–2 g calcium (10% $CaCl_2$ solution) over 5 min in adults; 20–30 mg/kg per dose in children (may repeat).
	Insulin[c]	IV: 0.5–1 U/kg bolus followed by 0.5–1 U/kg per h continuous infusion.
	Glucose	IV: 25 g (as 50 mL of $D_{50}W$) in adults; 0.5 g/kg (as $D_{25}W$) in children (to maintain euglycemia in patients treated with insulin).
Cyanide, hydrogen sulfide	Sodium nitrite	IV: 300 mg over 2–5 min in adults; 0.2 mL/kg over 2–5 min in children.
	Sodium thiosulfate	IV: 12.5 g bolus in adults; 0.5 g/kg bolus (maximum 12.5 g) in children.
	Hydroxocobalamin (preferred)	IV: 70 mg/kg over 15 min.
Digitalis glycosides	Digoxin immune Fab	IV: 10–20 vials over 30 min for acute empiric dosing, otherwise based on serum digoxin concentration if known.
Ethylene glycol, methanol	Fomepizole (preferred)	IV: 15 mg/kg over 30 min, then 10 mg/kg q12h × 4 doses, then 15 mg/kg q12h as needed until nontoxic.
	Ethanol	IV: 10 mL/kg of 10% vol/vol solution, then 1.5 mL/kg per h continuous infusion until nontoxic; double rate during dialysis.
Iron	Deferoxamine	IV: start 5 mg/kg per h continuous infusion and titrate to 15 mg/kg per h as tolerated, total daily dose 6–8 g.
Isoniazid, hydrazine, and monomethylhydrazine	Pyridoxine	IV: 5 g in adults; 1 g in children.

Lead	Dimercaprol (BAL)	IM: 75 mg/m^2 q4h, first dose to precede edetate calcium disodium ($CaNa_2$ EDTA). Contraindicated if peanut allergic.
	$CaNa_2$ EDTA	IV: 1500 mg/m^2/d by continuous infusion.
	Succimer (DMSA)	PO: 10 mg/kg q8h for 5 d, then q12 h for 14 d in adults; 350 mg/m^2 in children (same course).
Methemoglobin-forming oxidants	Methylene blue	IV: 1–2 mg/kg over 5 min with 30 mL fluid flush, may repeat 1 mg/kg once.
Methotrexate	Folinic acid (leucovorin)	IV: 100 mg/m^2 over 15–30 min q3–6h for several days with absence/resolution of bone marrow toxicity.
Neuroleptics	Bromocriptine	PO: 5 mg q12h increasing to effect, as high as 10 mg q6h.
	Dantrolene	IV: 3–10 mg/kg over 15 min with oral doses of 25–600 mg/d to maintain response.
Opioids and centrally acting α2 agonists (eg, clonidine, guanfacine, tizanidine)	Naloxone	IV: Start 0.05 mg with repeat dosing every 15 s to reversal of respiratory depression and/or unconsciousness; once achieved, repeat the same total dose q1h prn. Higher doses (1–2 mg or more) may be useful in α2-adrenergic agonist toxicity.[7]
Organophosphates and carbamates	Atropine	IV: 1–2 mg doubled every 3–5 min until bronchorrhea resolves in adults; 0.03 mg/kg in children, similar titration.
	Pralidoxime (2-PAM)	IV: 1–2 g over 30 min, then up to 500 mg/h in adults; 25–50 mg/kg over 30–60 min, then 10–20 mg/kg per h in children.[d]
Snakebite (rattlesnake, copperhead, cottonmouth)	*Crotalidae* Polyvalent Immune Fab	IV: 4 vials typical minimum first dose in normal saline. Scheduled and prn regimens are effective going forward.
Sulfonylureas	Octreotide	SC: 50 μg q6-12h in adults, 1.25 μg/kg (max 50 μg) q6h in children.
Tricyclic antidepressants (and related compounds with sodium channel blocking properties)	Sodium bicarbonate	IV: 50 mEq per dose to address acidemia and/or ECG signs of sodium channel blockade. For an isotonic solution to continue alkaline fluid resuscitation, mix 150 mEq $NaHCO_3$ (typically 3 ampules) and 40 mEq KCl in 1 L D_5W. Goal serum pH 7.5–7.55.
Valproic acid	L-Carnitine	Clinically ill: IV: 100 mg/kg (max 6 g) over 30 min, then 15 mg/kg q4h. Clinically well: PO: 100 mg/kg per d (max 3 g) divided q6h.

Abbreviations: D_5W, a solution of 5% dextrose in water; $D_{25}W$, a solution of 25% dextrose in water; $D_{50}W$, a solution of 50% dextrose in water; ECG, electrocardiogram; IM, intramuscular; INR, international normalized ratio; IV, intravenous; PO, by mouth; NG, nasogastric; prn, as needed; q, every; SC, subcutaneous.

[a] This is one of many N-acetylcysteine regimens in use in the United States. The best regimen to use in different clinical situations remains under investigation.

[b] Intravenous lipid emulsion has been used in patients critically ill from a variety of different toxins using varying regimens.

[c] Glucagon is still used as a diagnostic aid in beta-blocker poisoning, but has largely been supplanted by other agents, including high-dose insulin, for ongoing treatment.

[d] Use of pralidoxime in carbamate poisoning is controversial, as there is some concern for worsening muscular weakness.

Anticholinergics

The anticholinergic syndrome occurs frequently because many common medications and other xenobiotics have anticholinergic properties. From sleep aids to muscle relaxants to antipsychotics, almost any medicinal compound whose generic moniker ends in "-pine," "-zine," or "-amine" has the potential to disrupt cholinergic function in the CNS with resulting delirium. Polypharmacy is a major concern, particularly in the elderly, as a number of commonly used drugs not typically classified as anticholinergics do have the potential to interfere with this critically important neurotransmitter.[8] Cholinergic activity is the primary mediator of attention, concentration, memory, reasoning, planning, and, to a large extent, communicating and understanding through language. Antimuscarinic toxicity in the CNS causes delirium, frequently accompanied by mumbling speech and carphology, aimless "picking" movements of the fingers. Psychomotor activity is generally of high frequency and low amplitude when patients are awake. Vivid visual hallucinosis of living creatures occurs. Deep tendon reflexes are often hyperdynamic, with a few beats of inducible clonus not uncommon. Other peripheral effects also are observed, but because most anticholinergics are lipophilic, the impact on brain function may be much more evident than effects on other organ systems. Inhibition of secretory functions of the integument can yield dry mouth, flushed skin, and impaired heat dissipation, so undressing behavior in a state of confused discomfort is common.[9] Suppression of cholinergic inhibition of heart rate may produce tachycardia. Unopposed sympathetic drive of the ciliary apparatus produces pupillary dilation. Cholinergic function also is required for normal peristalsis and bladder emptying, so this syndrome may be accompanied by fecal and urinary retention, as well. The duration of CNS effects typically exceeds that of peripheral symptoms[10] due to the chemical preference of the toxins for fatty tissues and their slow diffusion back out of the central compartment once they have accumulated there.

Most patients recover with removal of offending agents and supportive therapy, but delirium may last for days after an acute overdose of anticholinergics, and considerably longer if medications that contribute to the problem continue to be administered. Physostigmine may be a useful diagnostic tool and may serve as an efficacious antidote to rapidly target the cause of delirium. This tertiary amine readily crosses the blood-brain barrier and makes more acetylcholine available for neuronal function via reversible inhibition of cholinesterase within approximately 15 minutes of an intravenous (IV) dose. However, the antidote is relatively short-acting, with a plasma cholinesterase inhibition half-life of less than 90 minutes.[11] Therefore, even though its lipophilicity may prolong restorative effects in the CNS, repeat dosing of physostigmine is typically necessary in the setting of severe anticholinergic toxicity.

Physostigmine is indicated in patients with anticholinergic delirium caused by a variety of compounds from prescription medications to botanic hallucinogens (eg, Jimson Weed) (**Box 1**). Primarily on the basis of 2 case reports of asystole,[12] its use has been curtailed in the setting of a possible tricyclic antidepressant (TCA) overdose or possible polysubstance toxicity. However, more than 3 decades of extensive clinical experience since then have documented its safety and utility in anticholinergic states induced by medications that affect cardiac conduction.[13,14] The largest study to date (nearly 1200 patients, many with polydrug overdoses) found no induced arrhythmias and a low incidence of precipitated seizures with proper weight-based dosing: 0.05 mg/kg IV at a rate not to exceed 0.5 mg/min, with doses no more frequent than hourly.[15] Patients were confused and/or sedate, not profusely diaphoretic, and potentially exposed to an anticholinergic agent; no other contraindications were

Box 1
Antimuscarinic compounds for which physostigmine is antidotal

"Pure" anticholinergics
- Atropine
- Scopolamine
- Hyoscyamine

Cyclic antidepressants
- Doxepin
- Amitriptyline
- Nortriptyline
- Imipramine
- Clomipramine
- Desipramine
- Protriptyline
- Amoxapine
- Maprotiline

Antiparkinson agents
- Benztropine
- Trihexyphenidyl
- Biperiden

Antispasmodics
- Dicyclomine
- Oxybutynin
- Tolterodine
- Propantheline
- Clidinium

Muscle Relaxants
- Baclofen
- Carisoprodol
- Cyclobenzaprine
- Orphenadrine
- Glutethimide

Antihistamines
- Hydroxyzine
- Diphenhydramine
- Doxylamine
- Pyrilamine
- Chlorpheniramine
- Brompheniramine
- Clemastine

Antiemetics
- Promethazine
- Prochlorperazine
- Meclizine
- Dimenhydrinate

Antipsychotics
- Quetiapine
- Olanzapine
- Clozapine
- Asenapine
- Loxapine
- Chlorpromazine
- Fluphenazine
- Trifluoperazine
- Perphenazine
- Thioridazine

Mesoridazine
Thiothixene

Botanicals[a]
Jimson weed (*Datura stramonium*)
Angel's trumpet (*Brugmansia* spp)
Deadly nightshade (*Atropa belladonna*)
Mandrakes (*Bryonia alba* and *Mandragora spp*)
Henbane (*Hyoscyamus niger*)
Bittersweet (*Celastrus scandens*)
Lupins (*Lupinus* spp)
Fly agaric (*Amanita muscaria*)

[a] Potentially beneficial for central nervous system manifestations of exposure to all plants in the family Solanaceae.

imposed. In this study, more than 80% of patients had a positive response to antidotal treatment, and no serious adverse effects were observed. More than 300 patients were poisoned with TCAs, and roughly 95% of those individuals benefited from physostigmine. Side effects may include enuresis, stooling, nausea, and vomiting; they are transient, but keeping the head of a patient's bed elevated is advised. A baseline electrocardiogram (ECG) is recommended, and if terminal right axis deviation is present (indicated by elevation of the R-wave in lead aVR) or frank widening of the QRS complex is observed, then pretreatment with an IV dose of lorazepam is recommended right before a test dose of physostigmine to prevent seizures.[16] Bradyarrhythmias are rare, but cardiac monitoring is suggested by some toxicologists,[17] and required by many hospital pharmacy policies.

Cholinergics

The cholinergic syndrome is uncommon, but important to recognize because life-saving treatment is available. Cholinergic toxicity produces a patient who presents "wet," as opposed to the anticholinergic syndrome, which often causes the patient to be "dry." The wetness is manifest by profuse sweating and excessive activity of the exocrine system, often accompanied by vomiting, diarrhea, and urinary incontinence. The mnemonic "SLUDGE" highlights specific elements of the syndrome: *s*alivation, *l*acrimation, *u*rination, *d*efecation, *g*astrointestinal cramping, and *e*mesis. The CNS (eg, confusion, seizures, coma) and skeletal muscles (eg, weakness, fasciculations, hyporeflexia) also can be involved, so the neuropsychiatric examination is important in diagnosis. Cholinergic excess is frequently caused by accidental organophosphate or carbamate pesticide exposure, which may occur through dermal contamination.[18] Such commercial/industrial agents and cholinesterase inhibitors used therapeutically for dementia can be used in suicide attempts, as well. Cholinergic effects also are the cause of toxicity from "nerve gases" like sarin and from mistaken ingestion of *Clitocybe* and *Inocybe* mushrooms. A not uncommon scenario of milder toxicity (but presenting with delirium) is accidental self-poisoning by a patient with dementia who takes repeat doses of a cognitive-enhancing drug due to forgetfulness about medication adherence.[19] It is also possible to develop toxic cholinergic "rebound" after abrupt cessation of excessive misuse of medications with anticholinergic properties (eg, diphenhydramine, quetiapine).[20] Mild forms of the toxidrome can be managed with discontinuation of offending agents and/or resumption of tapering doses of the overused anticholinergic drug, with supportive care. Recognition of critical illness should prompt the use of atropine (or perhaps glycopyrrolate if CNS

manifestations are not significant) and, in some cases of severe toxicity, the cholinesterase regenerator pralidoxime.[21]

Sedative/Hypnotics

When administered in sufficient dosage, sedative/hypnotics cause general anesthesia with diminished reflex activity and a complete loss of awareness. Sedation can be profound, but it is rare that benzodiazepine toxicity, alone, results in significant respiratory depression. Barbiturates, however, are sufficiently potent to produce shock and respiratory failure. "Pure" GABA-ergic toxidromes can sometimes be distinguished on the basis of history, lethargy or coma, relatively preserved pulmonary function, and the absence of constricted pupils (see **Table 1**). Patients also can be confused and disinhibited by benzodiazepines such that they display intermittent agitation, despite the CNS depression typically produced by these agents. This phenomenon, along with prolongation of delirial and comatose states, is a major iatrogenic complication of care in the ICU setting. Continuous infusions of midazolam remain common practice,[22] even though interrupted regimens have been associated with decreased sedative use, lower rates of delirium, fewer complications, and shorter lengths of stay; and thus appear in the most current practice guidelines for critical care.[23] Even intermittent use of benzodiazepines can yield neuropsychiatric complications with the potential to contribute to long-term sequelae, so recognition of and definitive treatment for sedative toxicity is critical.

When offending toxins operate at the benzodiazepine-binding site of the GABA-A receptor complex, reversal of this syndrome can be accomplished with the administration of flumazenil. It should not, however, be used in the setting of active toxicity from agents that are highly proarrhythmic or proconvulsant, because adverse events can result.[24] With careful attention to neurologic status and autonomic indices, physical examination can identify patients (non-hyperreflexic, without tachycardia or significant hypertension) who can safely receive a potentially therapeutic test dose of flumazenil. If individual IV doses are kept low (0.2–0.5 mg) and delivered over 30 seconds, the incidence of arrhythmias and seizures, even in patients who take benzodiazepines chronically, is negligible.[25] A state of anxiety may emerge from the reversal of stupor,[26] but supportive psychological presence is all that is required to manage such a side effect from the antidote.[25] Withdrawal is possible, but because such an outcome cannot be predicted and the effects will be transient, a low dose of flumazenil can be used safely[27] as an initial alternative to the standard practice, relatively lacking in an evidence base, of scheduling a protracted taper of benzodiazepines for all patients who have been sedated for extended periods in the ICU.[23,28] Therapeutic effects include facilitation of extubation, restoration of wakefulness and cognition, and relief of disinhibition with the result that patients can advance to calm participation in their own care. Flumazenil is short-acting; multiple doses may be necessary to maintain the effect, so after initial benefit is achieved, repeating 0.5-mg doses every hour as needed is recommended.[25]

Although their mechanisms of action differ somewhat from benzodiazepines, the toxic effects of nonbenzodiazepine sedatives (eg, zolpidem, zaleplon, and zopiclone) will respond to flumazenil. Flumazenil will not reverse either the effects of barbiturates or those of other sedatives that work via distinct mechanisms like ion channel modulation. Although not a specific antidote, as it is in the setting of benzodiazepine toxicity, flumazenil has been used with benefit in some cases of muscle relaxant overdose.[29] See **Box 2** for a list of toxins for which flumazenil may be antidotal. The suggestion of increased central GABA activity in the pathophysiology of hepatic encephalopathy

Box 2
Sedating compounds for which Flumazenil is antidotal

Benzodiazepines
- Lorazepam
- Oxazepam
- Temazepam
- Clorazepate
- Alprazolam
- Clonazepam
- Diazepam
- Triazolam
- Estazolam
- Midazolam
- Chlordiazepoxide
- Meprobamate
- Flunitrazepam

Muscle relaxants
- Carisoprodol (Meprobamate)[a]
- Metaxalone
- Chlorzoxazone
- Methocarbamol

Nonbenzodiazepines
- Imidazopyridines
  - Zolpidem
- Pyrazolopyrimidines
  - Zaleplon
- Cyclopyrrolones
  - Zopiclone
  - Eszopiclone

Botanicals
- Uncaria hook (*Uncaria macrophylla*)
- Yokukansan (*Uncaria rhynchophylla*)

[a] Meprobamate is a metabolite of carisoprodol with benzodiazepinelike GABA-ergic activity. The parent compound has anticholinergic activity and barbituratelike GABA-ergic activity.

and some limited clinical success indicate that flumazenil also may help to treat the neuropsychiatric complications of liver failure.[30]

Opioids

Toxicity from opioids progresses from analgesia to anesthetic CNS depression, coma, and death. Respiratory depression is particularly pronounced with opioid overdose, and the tidal volume or respiratory rate can be diminished before decreases in blood pressure or pulse occur. Sympatholysis is profound, and central to the toxidrome that leads to morbid and mortal outcomes with greater frequency than any other class of compounds.[31] Patients will have minimal respiratory drive and quickly develop manifestations of shock. Miosis also is characteristic and, in pure opioid toxicity, a fairly reliable finding.[32] A patient "found down" after several hours following opioid exposure will frequently have laboratory and imaging results consist with hypoxic and hypovolemic injury to multiple organ systems, including kidneys, liver, lungs, heart, skeletal muscle, and CNS. Damage to the latter is of greatest concern, as such injuries can leave patients who survive profoundly impaired and dependent on a high level of care indefinitely. In cases in which 4 or 5 days have passed since exposure, and

patients continue to display neurologic impairments in the absence of other obvious causes, MRI of the brain typically reveals hyperintensities on diffusion-weighted imaging (DWI) in watershed areas in patients with anoxic injury.[33] Injury patterns may vary, but involvement of perirolandic areas or even more diffuse DWI and T2 fluid-attenuated inversion recovery abnormalities typically indicate more severe CNS damage.[34] Although some patients, particularly those who are younger, can make remarkable recoveries despite strikingly abnormal MRI findings, imaging still can be helpful for assessment and initial treatment planning after the acute phase of toxicity has been addressed.

Patients with opioid toxicity require high-level critical care with aggressive fluid resuscitation and vasopressor support, especially if there is any significant delay in coming to treatment. Noncardiogenic pulmonary edema with progression to acute respiratory distress syndrome is common. Rhabdomyolysis combined with hypotensive renal damage can result in a need for hemodialysis, sometimes for weeks. Compartment syndrome can produce massive elevations in serum creatine kinase levels; this laboratory test abnormality will lag the time of damage by 8 hours or more, so it is important to perform a detailed physical examination of all major muscle groups at time of presentation after any significant “down time” to identify areas of vascular compromise. Areas of skin reddening or blistering, sometimes called ”barbiturate burns” can mark areas of prolonged pressure injury from time spent in deep coma.[35,36]

The diagnosis of opioid overdose is often confirmed using naloxone or nalmefene in adequate doses that reverse the toxidrome.[37] These mu receptor antagonists reliably reverse coma and respiratory depression if used shortly after an opioid overdose. Depending on the clinical scenario, lack of response is essentially diagnostic of another etiology for obtundation; in a patient with multisystem injury from opioid toxicity (see above), however, it is an ominous sign of prolonged CNS anoxia. Naloxone has an elimination half-life of approximately 1 hour, whereas that of nalmefene is more than 10 hours, thus making the latter antidote potentially useful in the case of opioid toxicity from a long-acting drug (eg, methadone).[38] In most patients, naloxone is the preferred agent, because a shorter-acting antidote allows for more careful titration of toxidrome reversal without precipitation of withdrawal. Medical toxicologists recommend assisted ventilation while preparing a low dose of 0.05 mg and then titrating upward every 15 seconds or so until an adequate response is achieved.[39] As soon as spontaneous respirations and calm wakefulness are restored, noting the total dose required is useful, because then the same naloxone dose can be repeated every 30 to 60 minutes as needed. Higher doses increase the likelihood of agitated withdrawal without added benefit to neurologic or respiratory status, especially in chronic users of opioids. Most opioids will require 0.4 mg or less of naloxone for adequate reversal. Exceptions include pentazocine[40] and buprenorphine,[41] partial agonists of mu receptors that have high binding affinity. The same may be true of some synthetic novel abusable opioids,[42] but an upward titration of antidote is still important to avoid dangerous withdrawal. Ongoing monitoring after antidote administration is vital, because cardiopulmonary symptoms are not reversed as durably as CNS depression, and life-threatening symptoms can recur.

Sympathomimetics

The sympathomimetic syndrome is usually seen after acute or chronic abuse of cocaine, amphetamines, or decongestants, the latter of which are often ingested in combination over-the-counter products. Pseudoephedrine and phenylephrine are the most common. Both are alpha-adrenergic agonists, with the former carrying

some beta-stimulatory activity as well.[43] Ephedrine has nonspecific adrenergic effects, and is found in herbal preparations used recreationally to enhance energy, or as adjuncts to fitness regimens.[44,45] Cathinones and related designer drugs of abuse also produce this toxidrome.[46] Ketamine, with its potential to increase the presynaptic release of catecholamines,[47] also can exacerbate sympathomimesis.

Blood pressure is elevated, the pulse is rapid, pupils are typically dilated, and piloerection may be seen. Mild toxicity rarely leads to cardiac complications, but large overdoses of sympathomimetic agents can produce hypertensive crisis, intracranial hemorrhage, arrhythmias, cardiovascular compromise, and shock. Seizures occur, and the postictal state can contribute to alterations in mental status. Some compounds (eg, cocaine) cause seizures and arrhythmias due to their ability to interact with neuronal and cardiac sodium channels,[48] so sodium bicarbonate infusions are essential in the critical care of severely poisoned patients. Otherwise, no specific antidotes exist. Symptomatic management and supportive care are required. Benzodiazepines serve as the cornerstone of acute treatment because they attenuate catecholamine release, alleviate hypertension, prevent seizures, and provide helpful sedation.[49] Beta-blockers tend to be used with caution, because they can leave alpha-adrenergic stimulation unopposed. Vasodilators, such as hydralazine, nitroprusside, or phentolamine, are typically preferred for treatment of severe hypertension that does not respond quickly to benzodiazepines. There has been some recent consideration of the alpha-2 adrenergic agonist dexmedetomidine to manage these cases by targeting the underlying pathophysiology of the toxidrome[50]; if used, doses should be kept in the range of high alpha-2 specificity ($\leq$0.5 μg/kg per hour) to avoid exacerbating hypertension via peripheral alpha-1 agonism.[51] Transition to clonidine or guanfacine may have a role after initial stability is achieved.

Patients may be agitated and even psychotic with manic symptoms and/or paranoid delusions.[52–54] The simple pharmacology and easy administration of haloperidol may make this agent preferable in the ICU management of these cases when an adjunct to benzodiazepines is needed. Psychiatric sequelae from some sympathomimetic toxins can linger long after physical symptoms have resolved, demanding attention to acute mental health care needs with subsequent abstinence and, sometimes, ongoing treatment with antipsychotic medications.[52] Atypical neuroleptics may be preferable once the critical illness period has passed, because they can have a more beneficial impact on mood, treat punding, and avoid movement side effects to which some patients may be more prone on account of their stimulant misuse.[55] As a general principle, it is important to appreciate that the clinical picture overlaps with serotonin syndrome, as these compounds have multiple mechanisms by which they enhance catecholamine activity.

Serotonergics

Serotonergic agents cause critical illness in various clinical scenarios, including suicidal overdoses, unintentional combined polypharmacy, and drug abuse misadventures involving cocaine, designer psychedelic stimulants, and dextromethorphan. The latter is a synthetic analog of codeine that is frequently abused by adolescents,[56] and is occasionally used alone or coingested with other compounds in suicide attempts. Its desirable and harmful effects are mediated by glutamatergic modulation and a collection of proserotonergic actions, including inhibition of serotonin reuptake mechanisms, direct serotonin receptor agonism, and even serotonin release.[57,58] Because most cases of serotonin syndrome can be traced to pharmacologic conditions in which more than 1 mechanism of serotonin enhancement is engaged,[59] it is not surprising that dextromethorphan alone can cause severe toxicity. As most

recreational drugs capable of producing euphoria or hallucinosis operate via serotonin release or direct agonism, abusing such a drug in the context of treatment with antidepressants is a common etiologic combination.[60] Bupropion, although not often classified as a robustly serotonergic drug,[61] produces a toxic overdose picture in which patients invariably meet clinical criteria for serotonin syndrome[62] and can be exceptionally sick.[63]

The serotonin toxic picture is one characterized by neuromuscular excess, hyperthermia, and altered mental status. Hyperactive delirium with high-amplitude psychomotor unrest of variable frequency is observed. Classic signs of lower extremity muscle rigidity, hyperreflexia, and especially robust ankle clonus help to distinguish this toxidrome from anticholinergic poisoning (see **Table 1**). Muscle breakdown from hypertonicity, severe agitation, and/or seizure activity is a serious concern. Metabolic acidosis is a serious threat to integrity of organ function. In contrast to anticholinergic poisoning, the skin is typically not dry and the abdomen not quiet, but the 2 toxidromes with their manifestations of delirium, hyperthermia, reactive tachycardia, hyperreflexia, and intermittent agitation can be difficult to distinguish on clinical examination alone. Failure of lethargy, confusion, and/or agitation to resolve with physostigmine can help to distinguish serotonin syndrome from anticholinergic delirium.[15] It is helpful to consider serotonergic toxicity on a continuum of severity, recognizing that relatively mild anxiety, paresthesias, akathisia, and/or tremor can be the result of drug side effects,[59] although, they can be hard to distinguish from underlying psychiatric problems for which the drugs may have been prescribed. This may be especially true in the ICU setting in which other drug effects are also in play, and intubation of patients interferes with their ability to communicate their symptoms, emotions, and perceptions. As a result, the commonly used "analgosedative" fentanyl cannot be recommended for use in toxicology patients in the ICU, as it is proserotonergic and can fuel a toxic delirial state in conjunction with antidepressants and other agents.[64]

Because the clinical picture of serotonin syndrome can mimic neuroleptic malignant syndrome (NMS), antipsychotic medications should be used with extreme caution in the initial management of this delirium if the exposure history is at all unclear. In addition to differences in precipitating medications, NMS typically results in more generalized and severe muscle rigidity without hyperreflexia.[59,65] Benzodiazepines treat restlessness and agitation in both conditions and can provide neuromuscular relaxation that reduces fever and prevents rhabdomyolysis and renal injury, even though cognitive impairment may persist. Benzodiazepines are, indeed, the cornerstone of treatment for serotonin syndrome to calm autonomic unrest, prevent arrhythmias and seizures, and reduce agitation.[59] Hyperthermia must be addressed with aggressive cooling techniques. Restraints must be avoided, as ongoing agitation with restricted movement can result in more heat generation, rhabdomyolysis, and lethal acidosis. When benzodiazepines are ineffective, barbiturates or propofol are used, occasionally augmented with paralytics.[59] The serotonin antagonist cyproheptadine has been used, but it requires oral dosing and therefore displays limited efficacy in the critical care setting[66]; it is also anticholinergic at higher doses, with the potential to worsen delirium and hyperthermia. Augmentation of therapy with antipsychotic agents that antagonize serotonin receptors (eg, chlorpromazine, risperidone) has been attempted, but with limited efficacy data and concerns about their accompanying pharmacologic activities.[59] As in toxic states of sympathomimesis, centrally acting alpha-2 agonists (eg, dexmedetomidine) are under consideration, especially in light of their lower deliriogenic potential as compared with benzodiazepines.[67] It is important to be aware that serotonin toxicity can persist well beyond the time when pharmacokinetic profiles of the offending agents might predict their clearance, because the

toxin in this syndrome is serotonin, and once a "storm" of neurotransmitter function has been incited, resolution depends not only on the exogenous substances but also on factors of physiology inherent to the patient.

Neuroleptics

Toxidromes involving antipsychotic medications can be variable and complex, reflecting the pharmacology of chemically diverse agents. Dopamine receptor antagonism is the central activity of all these drugs, but only high-potency, first-generation agents like haloperidol are likely to manifest a toxicity profile primarily reflective of that action. Many are anticholinergic, so in excessive doses, they may produce confusion and hallucinosis consistent with that toxidrome (see above), for which physostigmine is antidotal (see **Box 1**). It is also important to note, however, that although phenothiazines and newer, structurally unrelated antipsychotic medications have anticholinergic effects, they may not be sufficient to offset dopamine antagonism in the nigrostriatal pathway. As a result, movement disorder symptoms can accompany their use in therapeutic dose ranges. In these scenarios, anticholinergic agents, such as benztropine and diphenhydramine, are effective in reversing dystonias and acute parkinsonian effects. Noting this conundrum, we advise bearing in mind Paracelsus' foundational principle of medical toxicology, "*sola dosis facit venenum,*"[68] and approaching patients with suspected toxicity from neuroleptics differently based on the particular dosing and physiologic circumstances.

In the acute, purposeful overdose situation, patients are typically sedate with slowed motor activity from the effects of D2 antagonism, and also profoundly affected by anticholinergia if the agent in question has that activity. The latter will often be clinically dominant to the extent that use of physostigmine may help not only to clear confusion, but also to avoid intubation from concerns about obtundation.[15] Extrapyramidal effects (EPS) are rarely encountered in the setting of a suicidal ingestion of antipsychotic medication, whether it be a typical or atypical agent. The serotonin antagonism of atypical neuroleptics is not toxicologically relevant, apart from its potential to exacerbate sedation via mechanisms lacking a pharmacologic antidote; recovery comes only with tincture of time. Most neuroleptics have the capacity to antagonize alpha1-adrenergic receptors, so in conjunction with dopamine blockade (and in some cases, H1-histamine blockade), the result is hypotension. Fluid resuscitation is usually sufficient, although a brief period of vasopressor support may be necessary. Tachycardia may manifest from both alpha2-adrenergic blockade and anticholinergic effects. The greatest potential for lethality after a large ingestion of antipsychotic medication comes in the form of more serious arrhythmias.[69]

Although much attention has been paid to the differences between and among different compounds with respect to QT prolongation potential via potassium efflux antagonism,[70–72] the reality is that all antipsychotics come with a risk of *torsades de pointes* when taken in overdose.[73] The peak risk is observed, in most cases, approximately 6 hours after exposure; however, the greatest impact on myocardial rhythmicity can be delayed due to ongoing drug absorption after oral overdose. Management requires cardiac monitoring, supplementation with magnesium, and optimization of potassium and other electrolyte concentrations in serum. Sodium bicarbonate is not effective in preventing polymorphic ventricular arrhythmias; however, there are older antipsychotic medications capable of causing cardiac arrest via sodium channel blockade in similar fashion to TCAs. Thioridazine and mesoridazine overdoses will manifest with QRS widening on ECG, so treatment with sodium bicarbonate is central to prevention of ventricular arrhythmias in those cases,[74] along with

Box 3
Case study

A 27-year-old woman with schizoaffective disorder and addiction to alcohol and methamphetamine presented in near-coma to the intensive care unit (ICU) after suspected purposeful overdose of her psychiatric medications. Her prescriptions included olanzapine, fluoxetine, hydroxyzine, and gabapentin. Initially, she had a blood pressure of 136/73 mm Hg, heart rate of 111 beats per minute, a core temperature of 38°C, profound lethargy, purposeless movements of the arms with a tremor, and symmetric hyperreflexia with 1 beat of ankle clonus. Her electrocardiogram revealed no abnormalities apart from sinus tachycardia, and her laboratory studies were unremarkable. Without consideration of antidotal therapy, she was given benzodiazepines and then intubated with the procedure facilitated by succinylcholine and propofol. Infusions of propofol and fentanyl were maintained overnight, and then weaned down with a plan to extubate, because there was no discernible pulmonary pathology. Unfortunately, the patient exhibited agitated confusion. Instead of progressing to extubation under such circumstances, infusions were maintained at lower rates and she was given haloperidol in accordance with the ICU protocol for management of delirium. Records of the next physical examination document a blood pressure of 145/90 mm Hg, heart rate of 131 beats per minute, a core temperature of 38.1°C, and heightened reflexes with 4 beats of inducible ankle clonus. Critical care physicians recognized the potential problem of having given fentanyl to a patient with suspected recent exposures to fluoxetine and methamphetamine, and halted the opioid infusion. A few doses of 2 mg lorazepam were given on the second day in ICU. In the interest of minimizing the use of propofol, haloperidol doses were increased to 5 mg every 4 hours to manage agitation. Delirium persisted with no improvement on the third ICU day when the vital signs and neurologic examination were more in line with the initial presentation. Propofol was maintained in low-dose titration at the discretion of nursing staff, with a further increase in haloperidol to 10-mg doses as needed atop the previously scheduled regimen. On day 4 in the ICU, the patient's agitation was finally diminished, with breakthrough unrest only when her body was repositioned. Nursing staff noted her to be somewhat stiff when rolling for toileting, and paged medical staff about a fever of 39°C that afternoon. Acetaminophen was prescribed. A workup was undertaken for infectious causes of fever the next day; assays revealed a white blood count of 14/nL (increased over the 11/nL on admission) and broad-spectrum antibiotics were ordered. Vital signs were not severely abnormal, but varied over the course of the next day, while the body temperature remained above 39°C despite increase in fluid delivery and treatment with acetaminophen. The medication regimen was continued for another day until a psychiatric consultation was placed to "assist with management of prolonged delirium in the wake of a suicide attempt by a patient with drug abuse; no clear source of infection, not responding to haloperidol." A detailed interview, of course, could not be conducted, but the psychiatrist noted rigidity of all 4 limbs and normal deep tendon reflexes. A review of the medical record indicated that the patient had received a total of 125 mg haloperidol in the preceding 120 hours. A diagnosis of neuroleptic malignant syndrome (NMS) was proposed, with a recommendation to halt haloperidol, give sedative medications, institute aggressive cooling measures, and consider adding bromocriptine if rigidity were to persist. Abnormalities in vital signs, physical examination, and behavior became progressively less severe over the subsequent 6 days, and, despite developing a catheter-related urinary tract infection, the patient was finally able to leave the ICU nearly 3 weeks after her overdose.

The case highlights difficulties in managing the evolving course of a toxic patient in the ICU affected not only by a purposeful polysubstance ingestion, but also the medications used in critical care. There was a brief phase of serotonin toxicity due to the interaction between fentanyl and the compounds already present in the patient's tissues: fluoxetine and methamphetamine. Even though this toxidrome was quickly recognized, the less common problem of NMS eluded detection in the days following. Escalating doses of haloperidol created the problem, perhaps exacerbated by the olanzapine overdose. Attention to the vital signs and neuromuscular status would have provided guidance earlier in the clinical course and prevented the toxidrome from yielding a protracted ICU stay. Another point is that the patient's initial presentation was consistent with anticholinergic syndrome secondary to the effects of olanzapine, and physostigmine would have targeted the underlying cause of that confused agitation such that the subsequent iatrogenic toxic deliria could have been avoided.

attention to impaired repolarization. In general, older medications such as these are considerably more cardiotoxic in overdose than atypical agents.[69]

NMS is the potentially lethal complication that more commonly comes to mind in discussion of these medications. In the acute overdose scenario, however, NMS is extremely rare. NMS manifests under circumstances of ongoing treatment with antipsychotic medications, with the risk being higher during phases of escalating doses. The risk is also greater with high-potency dopamine blockers. Thus, a patient who has been prescribed neuroleptics and presents to hospital in an altered state of health and behavior, or a patient whose clinical picture changes significantly in the ICU after having been treated with neuroleptics, must have NMS on the list of differential diagnostic considerations. It may aptly be viewed as the most severe manifestation of the continuum of EPS (akathisia, dystonia, parkinsonism) that overwhelms whole-body neural homeostasis.[75] The toxidrome reflects an idiopathic reaction resulting in severe muscle rigidity, hyperthermia, autonomic instability, and altered mental status; it requires discontinuation of antipsychotic medication and aggressive symptom-focused medical interventions. Along with discontinuation of antipsychotics in favor of benzodiazepines, toxicologists recommend the use of dopamine receptor agonists (eg, bromocriptine) and turn to dantrolene sodium if severe muscle rigidity is fueling hyperthermia and/or rhabdomyolysis that will not respond to sedatives and paralytics.[76]

Noting the overlap of the features of NMS with serotonin syndrome (see above), the complexity of medication regimens in patients who may have these toxidromes, and the preference to avoid benzodiazepines[5] in favor of antipsychotic medications in the treatment of most delirial states,[77] efforts have been made to guide the process of distinguishing NMS from serotonin syndrome.[78] Unfortunately, these guidelines that highlight differences in white blood counts, transaminases, and fever intensity focus on the most critical forms of 2 toxidromes that present with a continuum of severity. In the interest of patient safety, NMS must be identified as early in its progression as possible, so that offending agents may be discontinued; and at these stages, laboratory indices and temperature readings are not helpful. On the other hand, a very inclusive set of criteria has been proposed that may deny many patients therapeutic benefit from neuroleptics if NMS is overdiagnosed.[79] Laboratory assays for urinary metabolites of dopamine and serotonin have been proposed to distinguish the syndromes,[80] but without validation or widespread availability of the technique, focus must turn to each individual patient's physical presentation. Two features of physical examination that must be assessed carefully and tracked repeatedly may be most helpful in defining cases of NMS: skeletal muscle tonicity and deep tendon reflex activity. Patients with muscular rigidity confined to the lower extremities along with hyperreflexia are very unlikely to have evolving NMS. This presentation is consistent with serotonin toxicity, especially if ankle clonus is present. Those individuals without hyperreflexia who have rigidity in all 4 limbs (even if fairly subtle) may indeed have early signs of toxicity from antipsychotic medication that could become very severe if the offending agents are not discontinued. In the ICU setting, making this distinction can be challenging; the case scenario outlines some of the complexities involved (**Box 3**).

SUMMARY

The toxidromes in this survey were chosen for review based on the combined variables of high epidemiologic frequency of cases in the ICU and availability of the drugs that cause them. Of course, there are countless other agents that can cause life-threatening complications. Inhalants and toxic alcohols are readily available substances involved in addiction that can produce critical illness from effects on cardiac, pulmonary, and neurologic

systems with psychiatric sequelae.[81–83] Over-the-counter products containing acetaminophen, nonsteroidal anti-inflammatory drugs, and aspirin frequently land purposeful overdose patients in the ICU.[84–86] Carbon monoxide exposure causes CNS injury that can lead to delayed neuropsychiatric impairment long after recovery from critical illness.[87–91] In addition to maintaining a basic familiarity with the principles of diagnosis and management and antidotes for these other poisons (see **Table 2**), it is worthwhile for the C-L psychiatrist to keep an updated medical toxicology handbook for reference.[92]

Although not qualified to deliver all the necessary treatments for toxicology patients in every setting, the psychosomatic medicine specialist can be well-equipped to identify toxidromes and investigate the underlying causes for them, as well. A thorough history (often gathered from several sources in the manner of a C-L psychiatrist) and astute physical examination are key to toxicologic diagnosis. As Georg Groddeck, by some called the father of psychosomatic medicine, suggested: the crucial question is "why" not merely "how" a particular disease state arises.[93]

In cases of suspected exposure, whether it be purposeful, accidental, or iatrogenic, toxidromic presentation that is consistent with the history should guide the judicious use of antidotes. Although surveys of available agents in the environment (eg, home, hospital ward) can be useful aids to the diagnostic process, the patient's vital signs and physical examination are the best guides to medical intervention. The focus of treatment always should be the patient and the patient's symptoms, not the toxin or the assays that may or may not discover it.[94] Good supportive care with prioritized attention to emergent physiologic needs is the cornerstone of management; detailed assessment and reassessment with synthesis of data over time is essential to this process. Removal of ongoing exposures and institution of selected treatments help to promote recovery from the toxicity of an ICU stay, and potentially reduce long-term impact on mental health and functionality.

REFERENCES

1. Davydow DS, Gifford JM, Desai SV, et al. Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. Gen Hosp Psychiatry 2008;30:421–34.
2. van den Boogaard M, Schoonhoven L, Evers AW, et al. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. Crit Care Med 2012;40:112–8.
3. Ingels M, Marks D, Clark RF. A survey of medical toxicology training in psychiatry residency programs. Acad Psychiatry 2003;27:50–3.
4. Flomenbaum NE, Goldfrank LR, Hoffman RS, et al. Principles of managing the poisoned or overdosed patient. In: Flomenbaum NE, Goldfrank LR, Hoffman RS, et al, editors. Goldfrank's toxicologic emergencies. 8th edition. New York: McGraw-Hill; 2006. p. 42–50.
5. Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis and treatment. Crit Care Clin 2008;24:657–722.
6. Donovan JW, Burkhart KK, Brent J. General management of the critically poisoned patient. In: Brent J, Wallace KL, Burkhart KK, et al, editors. Critical care toxicology: diagnosis and management of the critically poisoned patient. Philadelphia: Elsevier Mosby; 2005. p. 1–11.
7. Kulig K, Duffy J, Rumack BH, et al. Naloxone for treatment of clonidine overdose. JAMA 1982;247:1697.
8. Tune LE. Serum anticholinergic activity levels and delirium in the elderly. Semin Clin Neuropsychiatry 2000;5:149–53.

9. Maytal G, Smith FA, Stern TA. Naked patients in the general hospital: differential diagnosis and management strategies. Psychosomatics 2006;47:486–90.
10. Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry 2001;62:11–4.
11. Knapp S, Wardlow ML, Albert K, et al. Correlation between plasma physostigmine concentrations and percentage of acetylcholinesterase inhibition over time after controlled release of physostigmine in volunteer subjects. Drug Metab Dispos 1991;19:400–4.
12. Pentel P, Peterson CD. Asystole complicating physostigmine treatment of tricyclic antidepressant overdose. Ann Emerg Med 1980;9:588–90.
13. Burns MJ, Linden CH, Graudins A, et al. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. Ann Emerg Med 2000;35:374–81.
14. Schneir AB, Offerman SR, Ly BT, et al. Complications of diagnostic physostigmine administration to emergency department patients. Ann Emerg Med 2003; 42:14–9.
15. Rasimas JJ, Sachdeva KK, Donovan JW. Revival of an antidote: bedside experience with physostigmine. J Am Assoc Emerg Psychiatr 2014;12:5–24.
16. Boehnert MT, Lovejoy FH Jr. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. N Engl J Med 1985;313:474–9.
17. Martin TG, Morris WD. Physostigmine. In: Brent J, Wallace KL, Burkhart KK, et al, editors. Critical care toxicology: diagnosis and management of the critically poisoned patient. Philadelphia: Elsevier Mosby; 2005. p. 1565–74.
18. Hodgson MJ, Parkinson DK. Diagnosis of organophosphate intoxication. N Engl J Med 1985;313:329.
19. Greene YM, Noviasky J, Tariot PN. Donepezil overdose. J Clin Psychiatry 1999; 60:56–7.
20. Glickman L. Diphenhydramine abuse and withdrawal. JAMA 1986;256:1894.
21. Eddleston M, Szinicz L, Eyer P, et al. Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials. QJM 2002;95(5):275–83.
22. Anifantaki S, Prinianakis G, Vitsaksaki E, et al. Daily interruption of sedative infusions in an adult medical-surgical intensive care unit: randomized controlled trial. J Adv Nurs 2009;65:1054–60.
23. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263–306.
24. Seger DL. Flumazenil–treatment or toxin. J Toxicol Clin Toxicol 2004;42:209–16.
25. Rasimas JJ, Kivovich V, Sachdeva K, et al. Antagonizing the errors of history: bedside experience with flumazenil. J Am Assoc Emerg Psychiatry 2015;13:17–34.
26. Ngo AS, Anthony CR, Samuel M, et al. Should a benzodiazepine antagonist be used in unconscious patients presenting to the emergency department? Resuscitation 2007;74:27–37.
27. Breheny FX. Reversal of midazolam sedation with flumazenil. Crit Care Med 1992; 20:736–9.
28. Cammarano WB, Pittet JF, Weitz S, et al. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. Crit Care Med 1998;26:676–84.
29. Kim S. Skeletal muscle relaxants. In: Olson KR, Anderson IB, Benowitz NL, et al, editors. Poisoning and drug overdose. 5th edition. New York: McGraw-Hill; 2007. p. 341–3.

30. Ahboucha S, Butterworth RF. Pathophysiology of hepatic encephalopathy: a new look at GABA from the molecular standpoint. Metab Brain Dis 2004;19:331–43.
31. Mowry JB, Spyker DA, Brooks DE, et al. 2015 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd annual report. Clin Toxicol (Phila) 2016;54:924–1109.
32. Sporer KA. Acute heroin overdose. Ann Intern Med 1999;130:584–90.
33. White ML, Zhang Y, Helvey JT, et al. Anatomical patterns and correlated MRI findings of non-perinatal hypoxic-ischaemic encephalopathy. Br J Radiol 2013; 86(1021):20120464.
34. Muttikkal TJ, Wintermark M. MRI patterns of global hypoxic-ischemic injury in adults. J Neuroradiol 2013;40(3):164–71.
35. Holten C. Cutaneous phenomena in acute barbiturate poisoning. Acta Derm Venereol Suppl (Stockh) 1952;32:162–8.
36. Proudfoot AT, Donovan JW. Diagnosis of poisonings. In: Brent J, Wallace KL, Burkhart KK, et al, editors. Critical care toxicology: diagnosis and management of the critically poisoned patient. Philadelphia: Elsevier Mosby; 2005. p. 13–28.
37. Hoffman RS, Goldfrank LR. The poisoned patient with altered consciousness. Controversies in the use of a 'coma cocktail'. JAMA 1995;274:562–9.
38. Glass PS, Jhaveri RM, Smith LR. Comparison of potency and duration of action of nalmefene and naloxone. Anesth Analg 1994;78(3):536–41.
39. Hahn I-H, Nelson LS. Opioid antagonists. In: Brent J, Wallace KL, Burkhart KK, et al, editors. Critical care toxicology: diagnosis and management of the critically poisoned patient. Philadelphia: Elsevier Mosby; 2005. p. 1489–91.
40. Moore RA, Rumack BH, Conner CS, et al. Naloxone: underdosage after narcotic poisoning. Am J Dis Child 1980;134:156–8.
41. van Dorp E, Yassen A, Sarton E, et al. Naloxone reversal of buprenorphine-induced respiratory depression. Anesthesiology 2006;105:51–7.
42. Lucyk SN, Nelson LS. Novel synthetic opioids: an opioid epidemic within an opioid epidemic. Ann Emerg Med 2017;69:91–3.
43. Johnson DA, Hricik JG. The pharmacology of alpha-adrenergic decongestants. Pharmacotherapy 1993;13(6 Pt 2):110S–5S.
44. Food and Drug Administration, HHS. Final rule declaring dietary supplements containing ephedrine alkaloids adulterated because they present an unreasonable risk. Final rule. Fed Regist 2004;69(28):6787–854.
45. Nelson L, Perrone J. Herbal and alternative medicine. Emerg Med Clin North Am 2000;18(4):709–22.
46. Valente MJ, Guedes de Pinho P, de Lourdes Bastos M, et al. Khat and synthetic cathinones: a review. Arch Toxicol 2014;88:15–45.
47. Sleigh J, Harvey M, Voss L, et al. Ketamine–more mechanisms of action than just NMDA blockade. Trends Anaesth Crit Care 2014;4:76–81.
48. Beckman KJ, Parker RB, Hariman RJ, et al. Hemodynamic and electrophysiological actions of cocaine. Effects of sodium bicarbonate as an antidote in dogs. Circulation 1991;83:1799–807.
49. Young CC, Prielipp RC. Benzodiazepines in the intensive care unit. Crit Care Clin 2001;17:843–62.
50. Seyit M, Erdur B, Kortunay S, et al. A comparison of dexmedetomidine, moxonidine and alpha-methyldopa effects on acute, lethal cocaine toxicity. Iran Red Crescent Med J 2015;17:e18780.
51. Weerink MA, Struys MM, Hannivoort LN, et al. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet 2017. [Epub ahead of print].

52. Berman SM, Kuczenski R, McCracken JT, et al. Potential adverse effects of amphetamine treatment on brain and behavior: a review. Mol Psychiatry 2009; 14:123–42.
53. Dalton R. Mixed bipolar disorder precipitated by pseudoephedrine hydrochloride. South Med J 1990;83:64–5.
54. Lake CR, Tenglin R, Chernow B, et al. Psychomotor stimulant-induced mania in a genetically predisposed patient: a review of the literature and report of a case. J Clin Psychopharmacol 1983;3:97–100.
55. Rusyniak DE. Neurologic manifestations of chronic methamphetamine abuse. Psychiatr Clin North Am 2013;36:261–75.
56. Baker SD, Borys DJ. A possible trend suggesting increased abuse from Coricidin exposures reported to the Texas Poison Network: comparing 1998 to 1999. Vet Hum Toxicol 2002;44(3):169–71.
57. Burns JM, Boyer EW. Antitussives and substance abuse. Subst Abuse Rehabil 2013;4:75–82.
58. Chyka PA, Erdman AR, Manoguerra AS, et al. Dextromethorphan poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2007;45:662–77.
59. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352: 1112–20.
60. Kirschner RI, Cimikoski WJ, Donovan JW. Drug combinations associated with serotonin syndrome in patients admitted to a toxicology treatment center. Clin Toxicol 2008;46:612.
61. Foley KF, DeSanty KP, Kast RE. Bupropion: pharmacology and therapeutic applications. Expert Rev Neurother 2006;6:1249–65.
62. Dunkley EJ, Isbister GK, Sibbritt D, et al. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM 2003; 96:635–42.
63. Shepherd G, Velez LI, Keyes DC. Intentional bupropion overdoses. J Emerg Med 2004;27:147–51.
64. Pedavally S, Fugate JE, Rabinstein AA. Serotonin syndrome in the intensive care unit: clinical presentations and precipitating medications. Neurocrit Care 2014; 21:108–13.
65. Caroff SN. Neuroleptic malignant syndrome. In: Mann SC, Caroff SN, Keck PE, et al, editors. Neuroleptic malignant syndrome and related conditions. 2nd edition. Washington, DC: American Psychiatric Publishing; 2003. p. 1–44.
66. Isbister GK, Buckley NA, Whyte IM. Serotonin toxicity: a practical approach to diagnosis and treatment. Med J Aust 2007;187:361–5.
67. Constantin JM, Momon A, Mantz J, et al. Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. Anaesth Crit Care Pain Med 2016;35:7–15.
68. Deichmann WB, Henschler D, Holmsted B, et al. What is there that is not poison? A study of the Third Defense by Paracelsus. Arch Toxicol 1986;58:207–13.
69. Tan HH, Hoppe J, Heard K. A systematic review of cardiovascular effects after atypical antipsychotic medication overdose. Am J Emerg Med 2009;27(5):607–16.
70. Beach SR, Celano CM, Noseworthy PA, et al. QTc prolongation, torsades de pointes, and psychotropic medications. Psychosomatics 2013;54:1–13.
71. Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry 2001;158:1774–82.
72. Stöllberger C, Huber JO, Finsterer J. Antipsychotic drugs and QT prolongation. Int Clin Psychopharmacol 2005;20:243–51.

73. Hasnain M, Vieweg WV. QTc interval prolongation and torsade de pointes associated with second-generation antipsychotics and antidepressants: a comprehensive review. CNS Drugs 2014;28:887–920.
74. Buckley NA, Whyte IM, Dawson AH. Cardiotoxicity more common in thioridazine overdose than with other neuroleptics. J Toxicol Clin Toxicol 1995;33:199–204.
75. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry 2007;164:870–6.
76. Burns MJ. Neuroleptic malignant syndrome. In: Brent J, Wallace KL, Burkhart KK, et al, editors. Critical care toxicology: diagnosis and management of the critically poisoned patient. Philadelphia: Elsevier Mosby; 2005. p. 305–13.
77. Trzepacz PT, Meagher DJ, Leonard M. Delirium. In: Levenson JL, editor. Textbook of psychosomatic medicine. 2nd edition. Arlington: APA Publishing; 2011. p. 71–114.
78. Perry PJ, Wilborn CA. Serotonin syndrome vs neuroleptic malignant syndrome: a contrast of causes, diagnoses, and management. Ann Clin Psychiatry 2012;24:155–62.
79. Gurrera RJ, Caroff SN, Cohen A, et al. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. J Clin Psychiatry 2011;72:1222–8.
80. Sokoro AA, Zivot J, Ariano RE. Neuroleptic malignant syndrome versus serotonin syndrome: the search for a diagnostic tool. Ann Pharmacother 2011;45(9):e50.
81. McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. Br J Clin Pharmacol 2016;81:505–15.
82. Tormoehlen LM, Tekulve KJ, Nañagas KA. Hydrocarbon toxicity: a review. Clin Toxicol (Phila) 2014;52:479–89.
83. Wu LT, Howard MO. Psychiatric disorders in inhalant users: results from the national epidemiologic survey on alcohol and related conditions. Drug Alcohol Depend 2007;88:146–55.
84. Hodgman MJ, Garrard AR. A review of acetaminophen poisoning. Crit Care Clin 2012;28:499–516.
85. Hunter LJ, Wood DM, Dargan PI. The patterns of toxicity and management of acute nonsteroidal anti-inflammatory drug (NSAID) overdose. Open Access Emerg Med 2011;3:39–48.
86. O'Malley GF. Emergency department management of the salicylate-poisoned patient. Emerg Med Clin North Am 2007;25:333–46.
87. Myers RA, DeFazio A, Kelly MP. Chronic carbon monoxide exposure: a clinical syndrome detected by neuropsychological tests. J Clin Psychol 1998;54:555–67.
88. Asian S, Karcioglu O, Bilge F, et al. Post-interval syndrome after carbon monoxide poisoning. Vet Hum Toxicol 2004;46:183–5.
89. Ku BD, Shin HY, Kim EJ, et al. Secondary mania in a patient with delayed anoxic encephalopathy after carbon monoxide intoxication. J Clin Neurosci 2006;13:860–2.
90. Lam SP, Fong SY, Kwok A, et al. Delayed neuropsychiatric impairment after carbon monoxide poisoning from burning charcoal. Hong Kong Med J 2004;10:428–31.
91. Weaver LK. Clinical practice. Carbon monoxide poisoning. N Engl J Med 2009;360:1217–25.
92. Olson KR, Anderson IB, Benowitz NL, et al. Poisoning and drug overdose. 7th edition. New York: McGraw-Hill; 2017.
93. Groddeck G. The meaning of illness. New York: International Universities Press; 1977.
94. Rainey PM. Laboratory principles. In: Flomenbaum NE, Goldfrank LR, Hoffman RS, et al, editors. Goldfrank's toxicologic emergencies. 8th edition. New York: McGraw-Hill; 2006. p. 88–108.