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Authors:

Timothy J. Meehan, MD, MPH, Fellow in Medical Toxicology, Toxikon Consortium, Clinical Instructor of Emergency Medicine, University of Illinois at Chicago College of Medicine.

Trevonne M. Thompson, MD, FACEP, Assistant Professor of Emergency Medicine, Associate Director, Division of Medical Toxicology, University of Illinois at Chicago College of Medicine.

Timothy B. Erickson, MD, FACEP, FACMT, FAACT, Professor of Emergency Medicine and Medical Toxicology, University of Illinois at Chicago College of Medicine.

Peer Reviewer:

Frank LoVecchio, DO, FACEP, Vice-chair for Research, Department of Emergency Medicine, Maricopa Medical Center, Medical Director, Samaritan Regional Poison Control Center, Phoenix, AZ.

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New Overdoses: The Latest Trends in Poisoning

Introduction

The face of the overdose patient has changed in recent years. Illicit use of prescription opioid medications is on the rise.[1] Death from both intentional and unintentional prescription opioid use is increasing.[2,3] Over-the-counter medications now must be included with "typical" street drugs.

This article will review the concept of toxidromes and the appropriate use of drug screening, and describe specific issues dealing with new overdoses, with a focus on over-the-counter (OTC) and prescription medications. While the authors discuss some overdose treatments, an in-depth review of antidotal therapy is beyond the scope of this paper. As such, references to articles referring to these issues have been provided within each section.

The General Approach to the Overdose Patient

The approach to the management of the overdose patient is two-pronged, with simultaneous and parallel processes. It starts with the ABCs — airway, breathing, and circulation. "DONT" is a mnemonic for dextrose, oxygen, naloxone, and thiamine. If a rapid glucose measurement reveals hypoglycemia, rapid correction is important. Decontamination should be considered when clinically appropriate. Enhanced elimination procedures such as hemodialysis may be efficacious in treating certain overdoses. Antidotes, when available, are focused treatment specific for the toxin. Early consultation with a medical toxicologist or regional poison center is prudent. At the same time, the physician should be obtaining a history and physical exam and look for specific toxidromes (discussed below). In addition, diagnostic tests should be drawn.

Toxidromes. A toxic syndrome, or toxidrome, is a constellation of signs and symptoms associated with a specific class of poisons. In cases of unknown overdose, toxidrome recognition can assist in making the diagnosis. In no particular order, the common toxidromes are cholinergic-muscarinic, cholinergic-nicotinic, sympathomimetic, opioid, and anticholinergic. (*See Table 1.*) Toxidromes are best recognized in the case of exposure or overdose of a single agent. Multiple-drug ingestions may present with an obscured clinical picture.

Drug Screens. The most commonly used and misunderstood test in the management of an overdose is the toxicology screen. Understanding the appropriate use of the qualitative urine drug screen and circumstances where serum or blood quantitative testing is appropriate will assist in the appropriate treatment and disposition of the overdose patient.

Toxicologic diagnoses and management strategies are largely based on the history, physical examination, and basic laboratory tests. While it is possible to measure blood, serum, or urine concentrations of many substances, this is often of limited usefulness. Some tests require long turnaround times or the use of an outside reference laboratory, limiting the real-time use of the information. The interpretation of toxin concentrations is difficult because many substances do

Executive Summary

- Massive overdoses may present differently than "typical" overdoses.
- Intubation of a patient with salicylate overdose may reduce the respiratory alkalosis, leading to increased toxicity.
- Overdoses on prescription opioids are more common — some will not show up on drug screens.
- Intravenous fat emulsion is a new treatment that has shown effectiveness for lipid-soluble substances such as local anesthetics.

not have established threshold levels of toxicity.

The most commonly used drug screen is a urine ELISA-based qualitative test. The drugs tested for vary by institution. Some commonly tested substances are listed in Table 2. The urine toxicology screen is not a comprehensive test and does not test for many drugs of abuse (such as pharmaceuticals and many of the new street drugs). Because the urine toxicology screen is a qualitative test, a positive result simply means that a threshold urine concentration has been met. This is not necessarily a marker of poisoning or clinical effect. Additionally, the urine drug screen generally tests for specific drug metabolites and has a wide range of false-positive and false-negative results.

Quantitative blood or serum testing is useful in cases where such information will predict or confirm toxicity or will otherwise guide therapy. Examples of such drugs are listed in Table 3. In a patient with an unknown overdose, consider serum acetaminophen testing. Acetaminophen is common in many over-the-counter and prescription medications, and overdose is often without signs and symptoms until hepatotoxicity has developed.

For further reading, the authors recommend reference 4.

Massive Overdoses

In recent years, a dramatic trend in overdoses has been observed in regard to the quantity and chronicity of drugs ingested for recreational and suicidal intent. Additionally, as patients become more habituated to specific agents, their tolerance increases, requiring higher doses to achieve a desired effect. As a result, the commonly recognized therapeutic pharmacokinetic data of drugs may be overwhelmed and altered by toxicokinetics. Overdoses of common OTC drugs that generally result in mild toxicity have been noted to result in profound CNS depression, respiratory failure, metabolic acidosis, and multiple organ failure when taken in massive doses. From a public health viewpoint, it is not certain whether this is due to wider availability of prescription drugs and OTC medications (Web availability and super stores dispensing up to 1,000 tablets per bottle) or the intent of self-harm being magnified by an increased prevalence of psychiatric disorders in our society with limited psychosocial resources for those in need, exacerbated by a failing economy.

Before discussing specific agents, a brief review of the utility of anion-gap analysis with poisoned patients is warranted. The differential diagnosis for an elevated anion gap acidosis is recognized by the mnemonic: METAL ACID GAP. (*See Table on card insert.*) Large overdoses of OTC analgesics are often associated with profound metabolic acidosis and high mortality rate. Gastric motility may be altered, with possible benefit from delayed or repetitive decontamination, and hemodialysis should be considered regardless of the agent's therapeutic pharmacokinetic properties since such a large amount of the drug may be present in the serum.

Massive overdoses of valproic acid,[5] verapamil,[6] nifedapine, atenolol,[7] topiramate,[8] chloroquine,[9] amantadine,[10] bupropion,[11] and insulin[12] can present with metabolic acidosis, altered mental status, cardiovascular collapse, and multi-organ failure.

Caffeine overdoses from weight-loss regimens and energy drinks are on the rise, producing multiple symptoms, most of which are commonly associated with an increase in adrenergic tone. These can include hypertension, tachycardia, dysrhythmias, and central nervous and skeletal muscle stimulation. Massive caffeine ingestion can result in neurotoxicity, seizures, cardiovascular collapse, and death.[13]

OTC Pain-reliever Medications

Aspirin and Salicylates. There were more than 20,000 reported aspirin and non-aspirin salicylate exposures in 2005, 64% of which required treatment in a health care facility. Of these exposures, 50% were reported as intentional overdoses, and 60 patients died.[14]

The signs and symptoms of salicylate toxicity can be subtle. In chronic ingestions, erratic absorption and elimination kinetics can result in devastating effects.[15] These patients often are agitated, with tachypnea, tachycardia, and hyperthermia. Initial laboratory test reveal a mixed metabolic acidosis with respiratory alkalosis; the lack of a respiratory alkalosis in these patients is an ominous finding.

Recent fatality data noted in Poison Control Center records describe a typical case:

• A 45-year-old male took 400 tablets of 325 mg ASA and was found in his home 5 hours later "cold, blind, and unable to hear." The initial ASA level was 98 mg/dL. In the ED, he suffered a cardiac

Table 1: Common Toxidromes

Cholinergic-Muscarinic
• Excess salivation and lacrimation
• Urinary frequency, incontinence
• Diarrhea, emesis
• Bradycardia
• Bronchorrhea
• Bronchospasm
• Lethargy
• Miosis
Cholinergic-Nicotinic
• Mydriasis
• Tachycardia
• Weakness
• Tremors, fasciculations
• Lethargy
• Seizure
Anticholinergic
• Hyperthermia
• Flushed, dry skin
• Mydriasis
• Delirium, hallucinations
• Tachycardia
• Urinary retention
Sympathomimetic
• Mydriasis
• Tachycardia
• Hypertension
• Hyperthermia
• Agitation
• Seizure
Opioid
• Miosis
• Bradycardia
• Hypotension
• Hypoventilation
• Lethargy

arrest and expired.[16]

These patients frequently arrive in the ED critically ill. Despite aggressive focused therapy including decontamination, enhancement of elimination with serum and urinary alkalinization, and initiation of hemodialysis, they can decompensate rapidly and fatally. Care must be taken when intubating these patients. Removal of their respiratory drive and its compensatory alkalosis will result in a greater acidemia, which can then enhance salicylate entry to the central nervous system and other tissues. This results in seizures, arrhythmias, and frequently death.[17]

Ibuprofen and NSAIDs. Ibuprofen is a common agent of ingestion, but significant toxicity in overdose in the vast majority of cases is uncommon.

• A 17-year-old female was found unresponsive in her bedroom by family and in close proximity to a large empty bottle of ibuprofen with 1,000 tablets of 200 mg each. The patient was comatose with a metabolic acidosis (pH 7.08) and hypothermia. Despite intensive care and hemofiltration, the patient expired.

• A 14-year-old male presented with apnea and cardiovascular collapse after ingestion of 50 g (250 tablets) of ibuprofen. Laboratory evaluation noted a widened anion-gap acidosis and elevated lactate levels. The patient developed hypotension, renal failure, pulmonary hemorrhage, and GI bleed. The patient was placed on ECMO and survived.[18]

These cases show that ibuprofen, although generally considered benign in small ingestions, can be dangerous and fatal in massive overdoses. Widened anion-gap metabolic acidoses occur from both the ingestion (ibuprofen is an organic acid) as well as from the marked tissue perfusion derangements, causing both a Type A and Type B lactic acidosis.

Acetaminophen. Acetaminophen (paracetamol) continues to be a leading cause of intentional and accidental poisoning resulting in profound hepatotoxicity, and has recently been shown to be the number-one reason for liver transplantation.[19-21] It is found in many combination preparations for cough, cold, flu, and decongestant therapy.[22] The U.S. Food and Drug Administration (FDA), concerned about the incidence of acute liver failure due to acetaminophen overdose, has considered mandating new labeling on acetaminophen packaging. It is also considering reducing the maximum daily dose from 4 g, banning acetaminophen-narcotic combination products, and changing the current maximum single dose of 1 g to prescription status, making 650 mg the highest recommended nonprescription dose.[23]

• An acute ingestion of 200 g with a peak recorded serum acetaminophen level of 1,614 mcg/mL was recently reported. The patient presented with early onset of coma, metabolic acidosis, and hypotension in the absence of significant hepatic injury. In addition to N-acetylcysteine (NAC) therapy, hemodialysis was performed to manage the acid-base disturbance.[24]

Prescription Analgesics

The prevalence of overdose deaths from opioids is increasing throughout the world. Heroin remains the predominant illicit opioid seen in the emergency setting. Methadone plays a major role because of its widespread use to treat opioid dependency, its high potency, and long duration of action. Increasingly, buprenorphine is being used as an alternative pharmacotherapy and, although apparently safer than methadone, it still has an inherent risk of toxicity when used with CNS depressants such as benzodiazepines or when injected.[25] Morphine continues to be the dominant analgesic; however, misuse of oxycodone, hydromorphone, hydrocodone, and fentanyl is on the rise. The semi-synthetic opioids may not be detected by the standard urine opiate screen. The synthetic agents such as methadone, fentanyl, and tramadol are typically not detected, and may need to be sent to specialized toxicology laboratories to ensure that these substances are appropriately detected.[26,27] Prescription opioid drug misuse appears to be disproportionately high in very small urban, suburban, and rural areas of the United States.[28]

OxyContin. OxyContin is a sustained-release form of oxycodone. This long-acting product usually does not include acetaminophen. Crushing and snorting the

Table 2: Substances Commonly Tested for in Urine Drug Screens

- Marijuana
- Cocaine
- Benzodiazepines
- Phencyclidine
- Amphetamine
- Opioids

Table 3: Examples of Common Substances that Can Be Tested in Blood or Serum

- Acetaminophen
- Salicylate
- Theophylline
- Lithium
- Lead
- Carboxyhemoglobin
- Methemoglobin
- Toxic alcohols (methanol, ethylene glycol)
- Certain anticonvulsants (carbamazepine, valproic acid, phenytoin)
- Digoxin

delayed-release tablets results in a rapid release of the drug, increased absorption, and high peak serum concentrations. Common street names include Hillbilly Heroin, Oxy's, and Poor Man's Heroin.

Beginning in 2000, widespread reports of OxyContin abuse surfaced. According to the Diversion and Addiction-Related Surveillance (RADARS) system, the prevalence of abuse was ranked in the following order: OxyContin > hydrocodone > other oxycodone > methadone > morphine > hydromorphone > fentanyl > buprenorphine. In terms of the magnitude of abuse, modest growth was seen with all analgesics monitored, but was most pronounced with OxyContin and hydrocodone. These results indicate that OxyContin abuse is a pervasive problem in the United States, along with a pattern of increasing prescription drug abuse.[29]

OxyContin overdose presents with a typical opioid toxidrome, including decreased respirations, miosis, hypothermia, bradycardia, hypotension, and altered mental status. The presence of coingestants can cloud the clinical picture. If OxyContin overdose is suspected, early ventilation and oxygenation should be administered, which is generally sufficient to prevent death. Even in the absence of a confirmation, cautious administration of naloxone — the opioid receptor antagonist and antidote for opioid toxicity — may have both diagnostic and therapeutic advantages.[30]

Methadone. Methadone is a synthetic opioid, used both as an analgesic in severe pain relief and in the treatment of opiate dependence. Its increased use has led to a substantial market in diverted methadone and a high number of deaths where the drug has been implicated. The principal mechanisms by which methadone causes death are: respiratory depression, aspiration, pulmonary edema, bronchopneumonia, dysrhythmias, and renal failure.[31]

During the past several years, there has been a rise in deaths involving prescription methadone. A study reviewed 176 fatalities ascribed to methadone toxicity between 2000 and 2004. Deaths rose from 6 cases in 2000 to 68 cases in 2003. Of the 95 cases with a known history of methadone use, 48% involved a prescription by a private physician.[32]

In Hennepin County, MN, methadone is one of the top 10 drugs reported in medical examiner-investigated deaths and one of the most commonly diverted pharmaceuticals. A total of 96 deaths due to methadone were identified in a 10-year period, with the majority being Caucasian males.[33]

According to one study, methadone fatality cases were significantly more likely to have benzodiazepines and less likely to have alcohol detected compared to heroin-related deaths. Methadone cases were significantly more likely to be diagnosed with pre-existing systemic pathology and multiple organ system pathology. Specifically, methadone cases were more likely to have cardiac, pulmonary, hepatic, and renal disease.[34]

Ingestions of opioid analgesics by children can lead to significant toxicity as a result of depression of the respiratory and central nervous systems. Methadone is the most toxic of the opioids, with doses as low as a single tablet leading to death. Due to the long half-life and high potency of methadone, all children who have ingested any amount of methadone should be observed in an ED and considered for hospital admission, especially if naloxone reversal is required.[35]

Methadone is increasingly prescribed for chronic pain, yet the associated mortality appears to be rising disproportionately relative to other opioid analgesics. Although many deaths are likely the result of respiratory depression, prolongation of the QT interval and torsades de pointes may be a contributing factor. As a result, most guidelines advise assessing for QT interval prolongation with an ECG in methadone toxicity.[36,37] Methadone is a potent blocker of the delayed rectifier potassium ion channel. This results in QT-prolongation and TdP in susceptible individuals, especially if another medication with activity at this channel or an inhibitor of methadone metabolism is added.[38]

Fentanyl. A deadly fentanyl epidemic has been reported recently in major cities across the United States and Europe.[39,40] Signs and symptoms of toxicity are similar to that of other opioids. Due to its synthetic nature, most conventional urine drug screens are unable to detect the drug.

In the 1960s, fentanyl was introduced as an intravenous anesthetic under the trade name of Sublimaze. Initially, fentanyl abuse was most common among health care professionals.[41] Illicit analogs have been manufactured in clandestine laboratories since the late 1970s. These analogs have been substituted for or combined with heroin, resulting in other fatal epidemics. In the 1980s and 1990s, the analog

alpha-methylfentanyl, known on the street as "China White," resulted in many U.S. and European deaths.[42-44] In the mid-1990s, the Duragesic patch was introduced and reached $1 billion in gross sales by 2004. In October 2002, the Russian military allegedly used an aerosolized fentanyl derivative against terrorists holding hostages in a Moscow theater.

Fentanyl derivatives often are sold in clear plastic bags stamped with a skull and crossbones. Most users report a less euphoric high associated with the drug and stronger sedative and analgesic effects than with other opioids. Because the effects of fentanyl are brief and rapid in onset, it is even more addictive than heroin. Some heroin dealers mix fentanyl powder with larger amounts of heroin in order to increase potency or compensate for low-quality heroin.

Numerous recent fentanyl-related deaths have been reported in several major American cities. During 2006-07, 348 fentanyl-related fatalities were identified in Chicago. In 2006, fentanyl was identified as the cause of death in 178 cases in Detroit. Reports indicate that fentanyl overdose was responsible for the hospitalization of 42 patients over one weekend in New Jersey. In Chicago, federal authorities arrested several members of a notorious street gang for preparing fentanyl for sale on the street. Since that time, a clandestine Mexican laboratory thought to be manufacturing and shipping illicit fentanyl to Chicago has been shut down by federal agents.[37]

Available in intravenous, oral, and patch formulations, the routes of administration of this drug vary. Recently, fentanyl has been developed into an effervescent tablet for buccal absorption, much like the Actiq lollipop, along with an inhaler and nasal-spray device for fast-acting pain relief.

Fentanyl-related fatalities demonstrate the desperate measures of some unfortunate individuals:

- A 32-year-old male died after chewing a fentanyl transdermal patch.[45]
- Two males, 29 and 40 years old, smoked 7 fentanyl transdermal patches. Both were found dead the following day.[45]
- A 38-year-old female opened and then injected the contents of one fentanyl patch. Despite aggressive supportive care with naloxone infusion and pressors, she rapidly expired.[46]
- A 41-year-old female was found unresponsive and was pronounced dead on arrival in the ED with 11 fentanyl patches on her skin.[47]
- A 4-year-old female was found unresponsive at home by her grandmother. Paramedics noted one fentanyl patch on the child and two additional patch marks. The grandmother had applied patches to relieve the child's pain. Of note, the child's urine toxicology screen was negative.[48]

These cases illustrate the dangers of diverting and misusing fentanyl preparations for both unintended patients and in unintended ways. Transdermal systems have drug reservoirs sandwiched in between layers of permeable plastic. These reservoirs may contain extremely high concentrations of the drug, as this is required to overcome the relatively impermeable skin barrier. Violating these delivery systems and smoking, injecting, or ingesting the drug at a single point in time can result in a much higher load than the patch is designed to deliver over several days. Additionally, children are quite susceptible to "leftover" patch toxicity. Even though there may not be enough drug to affect an adult, their lower weights can result in significant poisoning.[49,50] Other worrisome transdermal medications that can be fatal to children include estrogen, nicotine, nitroglycerin, clonidine, exelon scopolamine, and salicylates (Ben-Gay, Icy-Hot).

Opioids exert their effects by binding to a variety of receptors including mu, kappa, and delta. Management of opioid intoxication includes airway management and support, supportive care, and administration of opioid antagonists. Naloxone is an opioid receptor antagonist with a greater affinity for binding the opioid mu receptors than the opiates. However, its half-life is only approximately 1-1.5 hours. Due to fentanyl's high potency, higher doses of naloxone may be required to reverse the opioid intoxication.[51,52]

In May 2006, at the height of the fentanyl epidemic, our institution's naloxone supply was depleted, and suspected opioid-related overdose patients were diverted to other institutions for several hours until our naloxone supply could be replenished ("Narcan bypass"). In the future, other synthetic opioids much more potent and rapid in onset than fentanyl may become available:[53]

- Remifentanil: "Ultiva" (shortest-acting opioid available);
- Sufentanil: "Sufenta" (1000x more potent than morphine);
- Carfentanil: "Wildnil" (an animal tranquilizer 10,000x more potent than morphine).

Psychoactive Medications

Antidepressants. Antidepressant medications are used not only for depression, but also for chronic pain disorders and other alterations in mood, such as anxiety and bipolar disorder. It is thought that imbalance in one or more neurosignaling pathways is the cause of mood disorders. Excess neurologic tone in any of these pathways may result in the manifestation of symptoms consistent with a mood disorder. (*See Table 4.*)

Early antidepressant medications regulated these systems in a somewhat indiscriminate manner. Side effects were common and not restricted to a single pathway. For example, tricyclic antidepressants cause toxicity consistent with serotonergic and dopaminergic excess. These agents also affect central alpha and cholinergic receptors and peripheral sodium channels that result in hypotension, sedation and seizures, cardiovascular collapse, and death.

The newer antidepressants are more selective, allowing fine-tuning of the neurochemistry involved in alteration of mood. (*See Table 5.*) We now have selective serotonin reuptake inhibitors (SSRIs),

Table 4: The Biogenic Amines, Their Sources, Their Actions

Neurotransmitter	CNS Source	Effects
Dopamine	Substantia nigra	Fine motor control, cognition
Norepinephrine	Locus ceruleus	Alertness, arousal
Serotonin	Midline raphe	Mood cognition

Table 5: Antidepressant Pharmaceutical Classes

Class	Generic Name	Trade Name(s)
Selective Serotonin Reuptake Inhibitor	Citalopram	Celexa
	Escitalopram	LexaPro
	Fluoxetine	Prozac, Serafem, Symbyax (with olanzapine)
	Fluvoxamine	Luvox
	Paroxetine	Paxil, Pexeva
	Sertraline	Zoloft
Serotonin/ Norepinephrine Reuptake Inhibitor	Duloxetine	Cymbalta
	Venlafaxine	Effexor
	Desvenlafaxine	Pristiq
Norepinephrine/ Dopamine Reuptake Inhibitor	Bupropion	WellButrin, Zyban, Aplenzin
Others	Trazodone	Desyrel
	Mirtazapine	Remeron

serotonin-norepinephrine reuptake inhibitors (SNRIs), and norepinephrine-dopamine reuptake inhibitors (NDRIs) prescribed as either monotherapy or in combination to re-establish the balance among these biologic amines.

In overdose, these agents are generally safer compared to the agents of the past. Patients present with mental status depression and low-grade tachycardia generally requiring only supportive care. Given the alteration in mentation status, the authors do not recommend the routine use of activated charcoal, although it may be considered if a patient presents in the ED before the manifestation of their symptoms. Additionally, gastric lavage has been shown to be unreliable and cannot be recommended as a routine therapeutic maneuver.

An assymptomatic patient should be observed for 6 hours. However, certain antidepressant medications have idiosyncratic toxicities of concern when taken in higher than intended doses and may require longer periods of observation. (*See Table 6.*)

The serotonin syndrome (SS) is the result of serotonergic excess within the central nervous system (CNS). It typically manifests early in treatment, even after a single dose.[54] The syndrome exists on a spectrum that includes mental status changes, autonomic hyperactivity, and alterations in muscular activity (tremors, clonus, and hyperreflexia greater in the lower extremities). It can occur in up to 14% of patients who overdose on serotonergic medications[55] and is a clinical diagnosis. No laboratory analyses exist to suggest or confirm this diagnosis.

Management of SS is primarily supportive and involves removal of the offending agent, as well as aggressive attention to autonomic instability and hyperthermia. For mild cases, symptoms may be managed with benzodiazepine therapy.[56] For more severe cases, the authors recommend ICU-level monitoring and care. In these more severe cases, there may be a benefit to using the antihistamine cyproheptadine, as it also has antiserotonergic activity. This medication is only available in oral form, but can be crushed and passed through a nasogastric tube as a slurry. The dose is 8 mg initially, with repeat dosing of 2 mg every 2-4 hours until symptoms improve or a maximal dose of 32 mg daily is reached.

Hyperthermia in SS is a manifestation of the hyperadrenergic and hypermetabolic state caused by serotonergic excess. Unlike fever, hyperthermia in SS is not a centrally mediated response to manipulation of the thermoregulatory center; consequently, it will not respond to medications such as acetaminophen or NSAIDs. Treatment of hyperthermia requires an active approach using parenteral benzodiazepines as first-line therapy. These have been shown to have a significant survival benefit. In extreme cases refractory to benzodiazepine therapy, external cooling measures may be required. If these are also ineffective, intubation and paralysis should be considered. Succinylcholine should be avoided due to the potential for rhabdomyolysis and resultant hyperkalemia-induced cardiac arrhythmias.

Typically, SS will resolve within 24 hours; however, prolonged courses can be seen in cases of massive overdose or with agents with long elimination half-lives and/or active metabolites.

For further reading on this topic, the authors suggest reference 57.

Antipsychotics. Neuroleptic malignant syndrome (NMS) presents similarly to SS. Even though it manifests with alterations in mental status, autonomic instability, hyperthermia,

Table 6: Idiopathic Reactions

Drug	Effect	Observation Time*,**
Citalopram	Dose-dependent QTc prolongation with TdP Lowers seizure threshold	Half life of 30-36 hours
Escitalopram	Dose-dependent QTc prolongation with TdP (believe to be less so than with citalopram)	Half life of 20-30 hours
Bupropion	QRS prolongation Lowers seizure threshold	Half life of 10-20 hours
Venlafaxine	Lowers seizure threshold	Half life of 3-4 hours
* In all cases, extended release or controlled release preparations will significantly prolong half-life.		
** Half lives listed are for therapeutic doses; in toxic doses, these may be prolonged.		

and musculoskeletal abnormalities, its etiologic agents and underlying pathophysiology are not the same and require a different approach to diagnosis and management.

Antipsychotics cause their effects by modulating dopaminergic transmission in the CNS. The dopamine hypothesis states that an excess of dopaminergic tone is responsible for psychotic behaviors. By blocking certain dopaminergic receptors (D2), antipsychotics effectively dampen the signaling responsible for the positive symptoms of psychosis.

After the discovery that serotonergic systems were an important factor in treating the negative symptoms of schizophrenia, newer "atypical" agents were developed. With a focus on the serotonergic neurotransmission pathways — usually 5HT2a — these drugs act by balancing the dopaminergic/serotonergic ratio as opposed to purely blocking dopamine. One beneficial effect was a decrease in extrapyramidal effects; however, new patterns and symptom complexes in overdose have evolved. These newer antipsychotic agents not only affect serotonergic and dopaminergic pathways, but also have effects on other neurotransmitters that can result in atypical toxicities. (*See Table 7.*)

In overdose, patients often have depressed mental status and tachycardia.[58,59] Tachycardia in this setting is potentially worrisome due to the propensity of typical and atypical antipsychotics to prolong the QTc interval.[60-62] An ECG may reveal the presence of QTc prolongation. Abnormally long QTc may devolve into the ventricular arrhythmia known as torsades de pointes, although this has not yet been reported.[63] Prophylactic therapy is not available to prevent this occurrence, but constant vigilance can result in timely treatment should it occur. Treatment of antipsychotic-associated torsades des pointes would be the same as typical therapy — intravenous magnesium and overdrive pacing.

Atypical antipsychotics have long elimination half-lives, resulting in a prolonged symptoms. For example, aripriprazole elimination can range from 3-6 days in therapeutic dosing. This may be significantly prolonged in overdose when the heptaic P450 system responsible for its metabolism is overwhelmed. Finally, given their serotonergic activity, they have been reported to cause SS and may also manifest NMS.

Traditionally, NMS is defined as the presence of altered mental status, muscular rigidity, hyperthermia, and autonomic dysfunction, although it can occur on a spectrum, with abnormal mentation and rigidity preceding hyperthermia and autonomic changes. It is similar in presentation to SS, although instead of being due to an excess of neurotransmitter, it is the end result of dopamine depletion. As opposed to SS, there is greater muscular rigidity in NMS, and the time to onset tends to be longer and more indolent. NMS typically occurs after a patient has been on antipsychotic medications for a prolonged amount of time before having an overdose and/or dosage increase. SS, by comparison, can occur after a single overdose and typically occurs early in therapeutic treatment. (*See Table 8.*)

NMS has been considered to respond to bromocriptine, a dopamine agonist. Biochemically this makes sense, as increasing dopamine to overcome dopaminergic blockade would be desirable. However, clinical results have been mixed. Additionally, if bromocriptine is given to a patient who is actually manifesting SS and not NMS, the clinical picture may worsen as bromocriptine also increases serotonin release.

Dantrolene is a peripherally acting muscle relaxant that is the cornerstone of therapy for the pharmacogenetic syndrome known as malignant hyperthermia (MH). MH is the result of administering halogenated general anesthetics to patients with a specific genetic deficiency in their muscular calcium storage/release mechanisms and is manifested by hyperthermia, rigidity, and rhabdomyolysis. Because of the similar presentation, dantrolene has been used in cases of NMS. However, the underlying pathophysiology is quite different. Dantrolene may decrease muscular hypermetabolism and does not have a specific antidotal effect. Additionally, expending the time and resources to obtain sufficient quantities of dantrolene to treat NMS at the expense of aggressive supportive care may be detrimental to patient outcome.

Table 7: Atypical Antipsychotics and Other Effects

Generic Drug	Alpha-1 Antagonism	Muscarinic Antagonism	Sodium Channel Blockade	Potassium Channel Blockade
Clozapine*	3+	3+	None known	1+
Olanzapine	2+	3+	None known	None known
Ziprasidone	2+	None known	None known	3+
Risperidone	2+	None known	None known	None known
Quetiapine	3+	3+	1+	1+
Aripriprazole	2+	None known	None known	None known
*Also binds avidly to the M4 muscarinic receptor, which may cause excessive sialorrhea.				
Alpha-1 antagonism: Can cause hypotension				
Muscarinic antagonism: Can cause the anticholinergic toxidrome				
Sodium channel blockade: Can cause QRS widening and cardiovascular instability; treatment is with sodium bicarbonate as with TCAs.				
Potassium channel blockade: Can cause QTc widening and cardiovascular instability; treatment is as one would treat torsades des pointes.				

Aggressive supportive care of NMS involves discontinuation of all dopaminergic medications — including the antiemetic metoclopramide — as well as utilization of benzodiazepines to control central sympathetic outflow and muscular hypermetabolism. If the patient remains hyperthermic despite adequate benzodiazepine therapy, active external cooling should be used. The hyperthermia often encountered is due to the hypermetabolic state and is not typically pathologic as seen with fevers; as such, antipyretics such as acetaminophen and NSAIDs would not be expected to work adequately to decrease the patient's temperature. Similar to SS, intubation and systemic paralysis may be required; succinylcholine should be avoided because of potential arrhythmias due to hyperkalemia.

Overall, the most appropriate intervention for both NMS and SS is the provision of aggressive supportive care. This entails early recognition of these syndromes, with removal of the offending agent(s), and institution of temperature control and metabolic protection. Additionally, these syndromes can cause a significant rhabdomyolysis; aggressive fluid and electrolyte management may ameliorate the renal damage. Ultimately, given the significant overlap between NMS and SS, as well as the possibility that the atypical antipsychotics may manifest a combination of both syndromes, the authors strongly suggest consultation with a medical toxicologist and/or regional poison control center for assistance in managing these patients.

Other Agents. Patients who overdose on lithium, valproic acid, or carbamazepine are potentially troubling cases to manage. Some patients may have leftover prescriptions available that they can coingest with their stated overdose. Unrecognized toxicity from lithium, valproic acid, and carbamazepine can have serious consequences and potentially fatal outcomes.[64] As a result, our toxicology service routinely recommends obtaining serum concentrations of all three agents (lithium, valproic acid, and carbamazepine) in patients who present with overdoses of any one of these medications.

Lithium. Ancient civilizations used to soak in lithiated springs for effects on mood, and it was present in the original formulation of 7-UP.[65] The therapeutic range is narrow, from 0.6-1.2 mEq/L, and elevated concentrations can result from acute or acute-on-chronic overdose, as well as chronic supratherapeutic ingestion. In overdose, it can cause gastrointestinal distress with dehydration, tremor, confusion, and renal injury. Absorption is slow, and patients may not manifest symptoms of overdose early. Distribution requires several hours to reach equilibrium, and elimination is exclusively renal. Hemodialysis is effective in removing lithium from the body. General recommendations for hemodialysis include serum concentrations greater than 4.0 mEq/L in acute ingestions (2.5 mEq/L with chronic toxicity), seizures, or profound mental status depression. Saline diuresis is effective in less severe ingestions, but patients who cannot tolerate high fluid loads may need hemodialysis. Overall, morbidity from missed diagnosis can be quite high, and includes renal failure.

Valproic Acid. Valproic acid is an anticonvulsant drug that has mood-stabilizing properties. Therapeutic levels typically fall between 50-100 mcg/mL. In overdose, it can present with evidence of hepatic injury, as well as obtundation both as a direct pharmaceutical effect and a result of interfering with the urea cycle. This causes an elevation in serum ammonia concentration that may complicate and compound the mental status effects. Despite the fact that protein binding is typically high, the binding sites are saturated in massive overdose, and a high level of free drug exists in the blood. Massive overdoses may respond to hemodialysis. Carnitine, an essential factor in fatty acid metabolism, has been reported to have benefit in these overdoses as valproic acid is metabolized in the mitochondria after being transported by carnitine.

Carbamazepine. Carbamazepine primarily affects the cardiovascular and neurologic systems in overdose. It possesses anticholinergic activity, and can thus delay its own absorption, resulting in late onset of symptomatology and adverse effects. Early signs of poisoning involve nystagmus and ataxia, and symptoms include nausea and mental

Table 8: Neuroleptic Malignant Syndrome vs. Serotonin Syndrome

Entity	VS	Time to Onset	Skin	Bowel Sounds	Muscular Tone	Reflexes	Etiology
Neuroleptic malignant syndrome	Hypertension, tachycardia, hyperthermia	Several days	Diaphoretic, pallid	Hypoactive	Rigidity ("lead pipe") in extremities	Hyper-reflexia	Dopamine depletion
Serotonin syndrome	Hypertension, tachycardia, hyperthermia	Less than 1 day	Diaphoretic	Hyperactive	Tremor, clonus (lower >upper)	Hyporeflexia	Serotonin excess

status depression. As the poisoning progresses and serum concentrations rise, cardiac conduction abnormalities may occur in both the QRS and QTc intervals. Neurologically, carbamazepine is pro-epileptogenic in supratherapeutic concentrations. The normal range is typically 4-12 mcg/mL, and profound neurologic effects and seizures are usually not seen unless the serum level exceeds 40 mcg/mL. Treatment is generally supportive, with benzodiazepines, barbiturates, or propofol as needed for seizures. Elimination can be enhanced through the use of multiple-dose activated charcoal, as the drug adsorbs avidly to charcoal and undergoes significant enterohepatic recirculation. As a result, this technique will interrupt reabsorption by the body and decrease the overall burden.

When patients with a history of bipolar disorder present due to a pharmaceutical overdose, one should not only check the appropriate serum drug concentrations based on the patient's ingestion, but should also consider obtaining levels on these 3 pharmaceuticals as a screening tool. If positive, they have the potential to change disposition.[67]

Intravenous Fat Emulsion ("Lipid Rescue")

No discussion of new overdose presentations could be complete without discussing a promising new antidote. Intravenous fat emulsion (IFE), also known commercially as Intralipid®, is a 20% lipid solution originally developed for hyperalimentation purposes. However, over the last several years, much research has shown its utility as an effective antidote with a wide margin of safety. Of important note, the use of IFE for the treatment of overdoses is currently an off-label indication, as it has not yet been approved by the Food and Drug Administration for this purpose.

The mechanism of action is not yet understood. The "lipid sink" theory suggests that infusions of IFE result in the creation of an intravascular lipid compartment into which highly lipid-soluble substances can diffuse. In theory, if these substances are sequestered into this fatty space, they are not available for release into tissue. Lower end-organ and tissue delivery results in lower rates of toxicity (dose-distribution-response).

The other theory involves the delivery of a highly energy-dense material to tissues and end organs during a period of extreme duress.

There are excellent data supporting IFE use for local anesthetics as well as an increasing number of case reports and series describing its use in overdoses involving highly lipid-soluble substances.[66,67] For example, it has been described for seroquel, bupropion, and beta-blocker overdoses.[68] While the latter has an accepted therapy (glucagon, hyperinsulinemia/euglycemia), the psychoactive medications are notoriously refractory to maximal supportive therapy in large overdoses. The introduction of IFE to the potential treatment algorithms for these medications requires further study but is promising in both its efficaciousness and safety profile.

• A 16-year-old female ingested 38 tablets of 300 mg quetiapine. She was transferred to the PICU in a stuporous state and was tachycardic and hypotensive. Her initial ECG revealed a QTc of 610 msec. Within 30 minutes of starting IFE therapy, her QTc had narrowed to 433 msec, and her mental status and hemodynamic profile both improved.[69]

Recent meta-analyses have shown benefits in animal models, but human data is lacking.[70,71]

Conclusions

The face of the overdose patient in an ED setting is changing. While we still evaluate and treat our "typical" heroin, cocaine, and ethanol poisonings, the increasing complexity and diversity of the pharmaceutical armamentarium has begun to alter the epidemiology of poisoning. Significant effects from OTC preparations are increasingly common. Delayed recognition of these ingestions can result in high morbidity and mortality, particularly if taken in massive amounts. Salicylate poisoning carries a high risk of death, especially if intubation is required, and poisoning from acetaminophen is now the leading cause of liver transplant in the United States.

With the increase in prescription opioids and pharmaceutical diversion, patient presentations with opioid poisoning are trending upward. If a drug screen is negative, it does not imply that there are no opioids present in the system.

Antipsychotics and antidepressants also are worrisome, with effects on several different neurosignaling pathways. While prediction of symptoms and toxicity can be done based on the general class of agent, several drugs have idiopathic toxicities that can cause seizures and arrhythmias, and can lead to death. Early

recognition of the neuroleptic malignant syndrome and serotonin syndrome are of paramount importance, but differentiation between the two is difficult.

Aggressive supportive care is often all that is required, although emerging evidence suggests that intravenous fat emulsion may be of great benefit in some patients if they have overdosed on a lipid-soluble pharmaceutical.

Ultimately, for the emergency physician, timely recognition of poisoning and rapid initiation of therapeutic maneuvers and aggressive supportive care are the cornerstones of overdose management. In these cases, we recommend obtaining assistance from your institution's medical toxicology service or from your local regional poison control center — from within the United States, the phone number is (800) 222-1222.

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Physician CME Questions

111. Which of the following is true regarding urine drug screens?
    A. They typically are quantitative.
    B. They typically test for all drugs of abuse.
    C. They confirm toxicity.
    D. They are qualitative and limited in scope.

112. Which of the following is the leading cause of liver failure requiring transplant?
    A. ethanol
    B. biliary carcinoma
    C. acetaminophen
    D. hepatitis

113. Which of the following is true of methadone?
    A. Children who ingest methadone should be observed.
    B. It is rarely encountered.
    C. Mortality is decreasing.
    D. Patients can be discharged immediately after a single dose of naloxone.

114. The appropriate treatment of hyperthermia in serotonin syndrome is:
    A. ibuprofen
    B. acetaminophen
    C. active cooling
    D. aspirin

115. Which of the following may suggest NMS over SS in a hyperthermic, altered patient?
    A. temperature > 105
    B. tachycardia
    C. excessive muscle tone
    D. hyporeflexia

116. The signs hypertension, tachycardia, mydriasis, and hyperthermia best describe which toxidrome?
    A. cholinergic-muscarinic
    B. sedative-hypnotic
    C. anticholinergic
    D. sympathomimetic

117. A patient arrives agitated and hyperthermic to 104 with a purported overdose of his "psych meds." Agitation control should be best accomplished with:
    A. benzodiazepines
    B. haloperidol
    C. physical restraints alone
    D. succinylcholine (as part of RSI)

118. Which is *not* a cause of an elevated anion-gap acidosis?
    A. ibuprofen
    B. salicylates
    C. acetaminophen
    D. oxycodone

119. When considering intravenous fat emulsion therapy for a poisoned patient, which of the following is *not* true?
    A. It may provide a "lipid sink" for lipid-soluble drugs to enter.
    B. It is FDA approved.
    C. It has been used safely for local anesthetic toxicity.
    D. It may provide an alternative energy source for tissues.

120. In a patient with an unclear overdose but a known history of mood disorder, which of the following commonly available serum drug concentrations will likely *not* be of benefit?
    A. phenytoin
    B. carbamazepine
    C. lithium
    D. valproic acid

CME Answers: 111. D; 112. C; 113. A; 114. C; 115. C; 116. D; 117. A; 118. D; 119. B; 120. A

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3. Apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication.	○	○	○	○	○	○
4. Discuss the differential diagnosis of the particular medical problems discussed in the publication.	○	○	○	○	○	○
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NEW OVERDOSES

111. A B C D 112. A B C D 113. A B C D 114. A B C D 115. A B C D 116. A B C D 117. A B C D
118. A B C D 119. A B C D 120. A B C D

Emergency Medicine Reports
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New Overdoses

Common Toxidromes

Cholinergic-Muscarinic

- Excess salivation and lacrimation
- Urinary frequency, incontinence
- Diarrhea, emesis
- Bradycardia
- Bronchorrhea
- Bronchospasm
- Lethargy
- Miosis

Cholinergic-Nicotinic

- Mydriasis
- Tachycardia
- Weakness
- Tremors, fasciculations
- Lethargy
- Seizure

Anticholinergic

- Hyperthermia
- Flushed, dry skin
- Mydriasis
- Delirium, hallucinations
- Tachycardia
- Urinary retention

Sympathomimetic

- Mydriasis
- Tachycardia
- Hypertension
- Hyperthermia
- Agitation
- Seizure

Opioid

- Miosis
- Bradycardia
- Hypotension
- Hypoventilation
- Lethargy

Substances Commonly Tested for in Urine Drug Screens

- Marijuana
- Cocaine
- Benzodiazepines
- Phencyclidine
- Amphetamine
- Opioids

Examples of Common Substances that Can Be Tested in Blood or Serum

- Acetaminophen
- Salicylate
- Theophylline
- Lithium
- Lead
- Carboxyhemoglobin
- Methemoglobin
- Toxic alcohols (methanol, ethylene glycol)
- Certain anticonvulsants (carbamazepine, valproic acid, phenytoin)
- Digoxin

Causes of Metabolic Acidosis with Widened Anion Gap

M Methanol, Metformin, Massive overdose
E Ethylene glycol
T Toluene
A Alcoholic ketoacidosis
L Lactic acidosis

A Acetaminophen
C CO, Cyanide, Colchicine
I INH, Iron, Ibuprofen
D DKA

G Generalized seizure drugs
A ASA salicylates
P Paraldehyde, Phenformin

The Biogenic Amines, Their Sources, Their Actions

Neurotransmitter	CNS Source	Effects
Dopamine	Substantia nigra	Fine motor control, cognition
Norepinephrine	Locus ceruleus	Alertness, arousal
Serotonin	Midline raphe	Mood cognition

Antidepressant Pharmaceutical Classes

Class	Generic Name	Trade Name(s)
Selective Serotonin Reuptake Inhibitor	Citalopram	Celexa
	Escitalopram	LexaPro
	Fluoxetine	Prozac, Serafem, Symbyax (with olanzapine)
	Fluvoxamine	Luvox
	Paroxetine	Paxil, Pexeva
	Sertraline	Zoloft
Serotonin/ Norepinephrine Reuptake Inhibitor	Duloxetine	Cymbalta
	Venlafaxine	Effexor
	Desvenlafaxine	Pristiq
Norepinephrine/ Dopamine Reuptake Inhibitor	Bupropion	WellButrin, Zyban, Aplenzin
Others	Trazodone	Desyrel
	Mirtazapine	Remeron

Idiopathic Reactions

Drug	Effect	Observation Time*,**
Citalopram	Dose-dependent QTc prolongation with TdP Lowers seizure threshold	Half life of 30-36 hours
Escitalopram	Dose-dependent QTc prolongation with TdP (believe to be less so than with citalopram)	Half life of 20-30 hours
Bupropion	QRS prolongation Lowers seizure threshold	Half life of 10-20 hours
Venlafaxine	Lowers seizure threshold	Half life of 3-4 hours
* In all cases, extended release or controlled release preparations will significantly prolong half-life.		
** Half lives listed are for therapeutic doses; in toxic doses, these may be prolonged.		

Atypical Antipsychotics and Other Effects

Generic Drug	Alpha-1 Antagonism	Muscarinic Antagonism	Sodium Channel Blockade	Potassium Channel Blockade
Clozapine*	3+	3+	None known	1+
Olanzapine	2+	3+	None known	None known
Ziprasidone	2+	None known	None known	3+
Risperidone	2+	None known	None known	None known
Quetiapine	3+	3+	1+	1+
Aripriprazole	2+	None known	None known	None known
*Also binds avidly to the M4 muscarinic receptor, which may cause excessive sialorrhea.				
Alpha-1 antagonism: Can cause hypotension				
Muscarinic antagonism: Can cause the anticholinergic toxidrome				
Sodium channel blockade: Can cause QRS widening and cardiovascular instability; treatment is with sodium bicarbonate as with TCAs.				
Potassium channel blockade: Can cause QTc widening and cardiovascular instability; treatment is as one would treat torsades des pointes.				

Neuroleptic Malignant Syndrome Vs. Serotonin Syndrome

Entity	VS	Time to Onset	Skin	Bowel Sounds	Muscular Tone	Reflexes	Etiology
Neuroleptic malignant syndrome	Hypertension, tachycardia, hyperthermia	Several days	Diaphoretic, pallid	Hypoactive	Rigidity ("lead pipe") in extremities	Hyper-reflexia	Dopamine depletion
Serotonin syndrome	Hypertension, tachycardia, hyperthermia	Less than 1 day	Diaphoretic	Hyperactive	Tremor, clonus (lower >upper)	Hyporeflexia	Serotonin excess

Supplement to *Emergency Medicine Reports*, May 24, 2010: "New Overdoses: The Latest Trends in Poisoning." *Authors:* **Timothy J. Meehan, MD, MPH,** Fellow in Medical Toxicology, Toxikon Consortium, Clinical Instructor of Emergency Medicine, University of Illinois at Chicago College of Medicine; **Trevonne M. Thompson, MD, FACEP**, Assistant Professor of Emergency Medicine, Associate Director, Division of Medical Toxicology, University of Illinois at Chicago College of Medicine; and **Timothy B. Erickson, MD, FACEP, FACMT, FAACT**, Professor of Emergency Medicine and Medical Toxicology, University of Illinois at Chicago College of Medicine.