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Drugs Of Abuse: Providing The Best In Evidence-Based Care To "Self-Medicated" Patients

It's the wee hours of a Sunday morning — or very late on a Saturday night, for some. The ED is finally quieting down. Just as you are about to have a seat and rest your sore feet, the ambulance bay doors swing open. On a stretcher, a 55-year-old woman appears, clutching her chest and clearly diaphoretic. She does manage to tell you that she has a history of hypercholesterolemia and hypertension and is not compliant with her medications. She received nitroglycerin and aspirin en route to the hospital, but with minimal relief.

The paramedics begin describing what they observed when they picked her up, but you are suddenly distracted by an alarm on the monitor. Her blood pressure is 190/110, and she is in sinus rhythm at 140 beats per minute. You need to lower that blood pressure and heart rate! A technician hands you an electrocardiogram with ST tombstones on the lateral leads, and you ask a nurse for a vial of metoprolol. You have only administered 5 mg of this medication, when suddenly the patient's blood pressure shoots up to 210/120, and she is clutching her chest and looking more anxious. The paramedics then tell you that they had observed several pipes and syringes lying around in her room.

Within seconds, the patient loses consciousness, and the monitor shows a ventricular tachycardia.

DRUGS of abuse frequently lead to ED visits for toxicity from intentional or accidental overdose, and occasionally for symptoms of withdrawal. Diagnosis may be difficult, as the history is often limited or unavailable. Treatment may be complicated by confounding factors, such as trauma, psychiatric disease, or drug-induced physiological disturbances (eg, cocaine-induced myocardial infarction (MI) or phencyclidine (PCP)-induced hyperthermia). Although challenging at times, the diagnosis and treatment of such patients is not impossible. Attention to airway, breathing,

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Authors

Marina Del Rios, MD
Department of Emergency Medicine, St. Luke's-Roosevelt Hospital Center—New York, NY.

Michael Lanigan, MD
Assistant Medical Director, Department of Emergency Medicine, St. Luke's-Roosevelt Hospital Center—New York, NY.

Vincent Zayas, MD
Department of Emergency Medicine, St. Luke's-Roosevelt Hospital Center—New York, NY.

Peer Reviewers

Lisa Freeman, MD, FACEP
Assistant Professor, Department of Emergency Medicine, University of Texas Medical School at Houston—Houston, TX.

Andy Jagoda, MD, FACEP
Professor and Vice-Chair of Academic Affairs, Department of Emergency Medicine; Residency Program Director, Mount Sinai School of Medicine—New York, NY.

CME Objectives

Upon completing this article, you should be able to:

1. Diagnose patients who are poisoned or intoxicated with substances of abuse.
2. Recognize the toxidromes associated with each major class of drugs of abuse.
3. Distinguish between patients requiring only supportive care, and those with more urgent or life-threatening conditions.
4. Treat and safely discharge patients based on your knowledge of the drug(s) ingested.

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and circulation — the mainstays of management for any ED patient — is the cornerstone of initial stabilization of intoxicated patients. The class of drug involved, if not the drug itself, can frequently be established by physical examination — and this information alone is often enough to guide appropriate interventions. Most of these patients will make a complete recovery, many while still in the ED. Unfortunately, others are at risk for deterioration and bad outcomes. This issue of *Emergency Medicine PRACTICE* highlights those drugs of abuse that are being seen most frequently in the ED today and provides an update on recognition and management that may be lifesaving for both the patient ... and your practice.

Critical Appraisal Of The Literature

Drugs of abuse that are also therapeutic compounds, such as ketamine and opioids, have a rich literature to describe their effects — although frequently not in the doses seen with recreational users. Other drugs, such as methylenedioxymethamphetamine (MDMA, or "ecstasy"), have few controlled trials to assess their effects. As a result, many publications on management of the intoxicated patient are based on retrospective case series and individual case reports; recommendations for the care of the intoxicated patient are generally consensus-based. A search of the National Guideline Clearinghouse, the Cochrane Database, and OVID did not identify any relevant practice guidelines.

Epidemiology

The US Department of Health & Human Services reported in their 2003 National Survey on Drug Use and Health (NSDUH) that an estimated 21.6 million Americans aged 12 or older were classified with substance dependence or abuse.[1] This survey also found that serious mental illness (SMI), as defined by the DSM-IV, correlated with illicit drug use. In 2003, adults with SMI were more than twice as likely as those without SMI to have used an illicit drug in the past year. Indeed, among adults with substance dependence or abuse, 21.6% had SMI, compared with an SMI rate of 8.0% among those who did not have substance dependence or abuse. The survey reported that 3.3 million people aged 12 or older received treatment for alcohol or illicit drugs in the 12 months prior to being interviewed. Of these, 251,000 received treatment at an ED.

According to the Office of National Drug Control Policy (ONDCP), substance-abuse–related health care costs — for prevention, substance abuse treatment, and treatment of the medical consequences of substance abuse — increased 2.9% per year between 1992 and 1998.[2] Health care costs in the US for substance-abuse–related illness reached an estimated $12.9 billion in 1998; in 2001, a total of 21,683 people died of drug-induced causes in the United States.[3]

The Drug Abuse Warning Network (DAWN) has gathered data on the top drugs resulting in an ED visit for patients older than the age of 6. (See **Table 1**.)[4] Drugs are classified into 1 of 5 schedules, based on the drug's medical use, potential for abuse, safety, and potential for dependence. (See **Table 2**.)[5]

Differential Diagnosis

The differential diagnosis for a patient presenting with drug intoxication depends in large part on the drug in question and the most prominent symptoms. Unfortunately, the same symptoms seen in other medical emergencies may also be seen in drug intoxication; for example, tachycardia and hypertension may be caused by cocaine use — but other possibilities include thyroid storm, pheochromocytoma, or an idiopathic hypertensive emergency. Contributing to the diagnostic challenge posed by these patients is that most present with alterations in mental status. As a result, the differential diagnosis is wide, including but not limited to: structural intracranial pathologies, stroke, complicated migraine headaches, hypoglycemia, electrolyte and blood sugar disorders, hypertensive encephalopathy, hepatic encephalopathy, hypoxia, uremia, and systemic and central nervous system infections. Psychiatric disorders are generally a diagnosis of exclusion in these patients.

Prehospital Care

Prehospital assessment and stabilization of the poisoned patient begins with securing the airway, breathing, and circulation, and considering cervical spine immobilization. A careful scene assessment is a critical role played by EMS and may provide the key to successful management. Pill bottles, drug paraphernalia, or other scene clues should

Table 1. 2002 DAWN Data: Major Substances Of Abuse (In Order Of Frequency) That Lead To ED Visits.

1. Alcohol (in combination with other substances)
2. Cocaine
3. Marijuana
4. Heroin
5. Amphetamines
6. Methamphetamine
7. PCP
8. MDMA (Ecstasy)
9. GHB
10. Inhalants
11. Miscellaneous Hallucinogens
12. LSD
13. Ketamine

*Source: Drug Abuse Warning Network, 2003: Interim National Estimates of Drug-Related Emergency Department Visits. See Reference 65.

either be noted by EMS or brought with the patients to the ED.

Prehospital care providers may also perform diagnostic/therapeutic interventions in patients with an altered sensorium. When possible, a fingerstick glucose should be obtained. If this is not possible, or if the glucose level is determined to be low, dextrose and thiamine should be given intravenously. If the patient has findings on physical examination that suggest an opioid overdose (see ED Evaluation section below), naloxone should be administered.

Management of agitated and/or combative patients is a major challenge for EMS, and either physical restraint or pharmacologic treatments must be considered. This complication is underscored by a study that found more than half of patients placed in restraints or seclusion in the ED arrived via the EMS system.[6] Physical restraint requires a high level of vigilance to avoid iatrogenic harm to the patient.[7] There is only 1 study that examined the prehospital use of chemical restraint: Rosen et al compared 5 mg of droperidol IV to placebo in 46 patients. There was significantly greater sedation with droperidol at 5 and 10 minutes, and no significant side effects, except 1 occurrence of akathisia that had no associated morbidity.[8] Nonetheless, since droperidol availability is limited, and the use of antipsychotic agents has been associated with increased risk of ventricular dysrhythmias in patients with prolonged QTc (see below), benzodiazepines are currently the best options for EMS.

ED Evaluation

Initial Stabilization

As with the prehospital assessment, the initial ED evaluation begins with assessment and stabilization of the airway, breathing, and circulation. If not assessed in the field, fingerstick glucose determination should be performed, and a naloxone challenge may be considered. The patient should also be placed on a cardiac monitor with continuous oxygen saturation monitoring.

History

Patients who are alert enough to identify the drug they used rarely pose a diagnostic dilemma. Frequently, however, obtaining a thorough history may be impossible, due to the patient's altered sensorium. In such cases, EMS personnel are an invaluable source of information. They can describe the scene, and possibly provide pills, pill bottles, or a suicide note that might identify the ingestion. They can relate anything that the patient or any bystanders told them about the event. If any friends or witnesses come to the ED, it is important to clarify what was learned initially and to seek further history, such as substance abuse, past medical and psychiatric history, medications, and allergies.

Physical Examination

A thorough physical examination should be performed after the patient has been stabilized. The patient should be fully undressed to look for additional clues, eg, needle track marks or signs of trauma. As part of this thorough examination, particular attention should be paid to findings that suggest a toxicologic syndrome ("toxidrome") — a constellation of signs that suggest intoxication with a particular class of drug. A toxidrome-focused physical examination may be performed quickly and easily, and may provide a diagnosis despite a paucity of historical information, and before laboratory tests have returned.

The toxidrome-focused physical examination consists of assessing all 4 vital signs, as well as mental status, pupil size, mucous membranes, lung sounds, bowel sounds, and skin.[9] In 1 study, nurses, medical residents, and pharmacists used the toxidrome-focused physical examination to determine the class of drug responsible for the clinical symptoms in 204 consecutive patients. Their accuracy was 88%, 84%, and 79%, respectively, which suggests that this examination has considerable utility in the evaluation of poisoned patients.[10] The important "toxidromes" are sum-

Table 2. Drug Scheduling.

Schedule	Characteristics	Examples
I	High potential for abuse, with no currently accepted medical use in the United States. Considered dangerous when used without medical supervision.	MDMA, ecstasy, marijuana, LSD, GHB, heroin
II	High potential for abuse, but with some accepted medical uses in the United States. Abuse leads to physical and/or psychological dependence and is considered dangerous.	Morphine, cocaine, PCP, opium
III	Potential for abuse, but lower than prior categories. There are accepted medical uses for these, and abuse can lead to mild or moderate physical dependence or great psychological dependence.	Ketamine, codeine combination products, lysergic acid (LSD precursor), anabolic steroids
IV	Drugs with relatively low potential for abuse. Have accepted medical uses in the US. Abuse leads to limited physical and psychological dependence.	Benzodiazepines, phenobarbital
V	Low potential for abuse, with accepted medical uses in the US. Abuse may lead to limited physical or psychological dependence.	Opioid preparations of antidiarrheal and antitussive medications

marized in **Table 3**.

Diagnostic Studies

The 2 most important bedside tests, which should be obtained immediately in any patient in whom drug intoxication is suspected, are a fingerstick glucose level and an electrocardiogram. The fingerstick glucose is important to exclude hypoglycemia, which may cause alterations in mental status ranging from coma and sedation to confusion or agitation.

In the setting of drug use or abuse, the ECG assessment should include an evaluation of the QRS and corrected QT (QTc) intervals. A prolonged QRS interval (> 100 msec) coupled with a rightward deflection of the terminal 40 milliseconds of the QRS complex (which manifests as a broad S wave in leads I and avL and a tall R wave in lead avR) suggests poisoning with a tricyclic antidepressant[11,12] or another agent that blocks fast sodium channels (such as cocaine). Prolongation of the QTc can be seen as an effect of many drugs, although not so frequently with street drugs. A prolonged QTc puts the patient at increased risk for ventricular dysrhythmias, including torsades des pointes, and thus is a relative contraindication for using typical or atypical antipsychotics.[13,14]

If the diagnosis of toxicity from a drug of abuse is certain and the substance is clearly identifiable, and if no other diagnoses are being entertained and the patient is stable, serum chemistries and other laboratory tests will likely be of no benefit. A blood alcohol level may be obtained if intoxication is suspected or, if suicidal intent is a possibility, acetaminophen and salicylate levels should be obtained.

The appropriate role for urinary "toxicology screens" is widely debated. Proponents note that this is a simple, noninvasive means of ascertaining the presence or absence of drugs or metabolites, and it may help to make a diagnosis or refine the differential diagnosis. Opponents, on the other hand, generally make 3 arguments against its use. First, urine toxicology testing only confirms exposure to a drug; it does not confirm that the patient's symptoms are due to that drug. For instance, a patient with severe alcohol withdrawal who used cocaine 2 days prior to presentation will have a positive "tox screen" for cocaine; it is important, therefore, that a laboratory result not be relied on as a substitute for clinical acumen. Secondly, cross-reactivities may lead to false-positive tests — this is the case with dextromethorphan, a common agent in over-the-counter cough preparations that may cause a false-positive result for phencyclidine (PCP). A third argument is that the test may be negative, despite a true drug intoxication: several PCP derivatives produce a clinical state indistinguishable from PCP intoxication, but they do not react with the urinary screen, and there are several opioids (eg, oxycodone, methadone, and fentanyl) that may fail to react with a hospital's opiate screen. A retrospective chart review of over 400 patients at a Level I trauma center revealed that none of the patients' immediate treatment plans were altered by a positive urine toxicology result.[15] However, the utility of urinary toxicology screening in adult trauma patients is for referral to rehabilitation programs and injury prevention efforts, and therefore it may be an appropriate test in certain specific circumstances.[16]

Substances Of Abuse

Diagnosing and treating intoxicated or poisoned patients requires knowledge of the major classes of substances

Table 3. Toxidrome-Focused Physical Exam Findings.

Group	Vital Signs	Mental Status	Physical Exam
Stimulants	Hypertension, tachycardia, hyperthermia, tachypnea	Hyperalert, euphoria	Mydriasis, increased peristalsis, diaphoresis, tremor
Sedative-hypnotics	Hypotension, bradycardia, apnea	Stupor, coma, slurred speech	Decreased peristalsis, hyporeflexia
Sedative-hypnotic withdrawal	Hypertension, tachycardia, tachypnea, hyperthermia	Hyperalert, anxious	Mydriasis, increased peristalsis, diaphoresis, nausea, tremors, seizures
Opioids	Hypotension, bradycardia, apnea and shallow breathing, hypothermia	Stupor, lethargy, coma	Miosis, decreased peristalsis, hyporeflexia
Opioid withdrawal	Hypertension, tachycardia	Normal to agitated, but oriented	Mydriasis, increased peristalsis, diaphoresis, hyperactivity, nausea, vomiting, rhinorrhea, piloerection
Hallucinogenics	Hyperthermia, hypertension	Agitated but oriented, psychosis, panic	Mydriasis, synesthesias
Dissociative Agents	Hypertension, tachycardia, hyperthermia	Disorientation, lethargy, body image distortion, hallucinations, coma, depersonalization	Miosis, nystagmus, ataxia, vomiting

most commonly abused. These classes are detailed in the sections that follow. For a drug-specific overview of the major clinical presentations and treatments, see **Table 4**.

Dissociative Agents

Phencyclidine (PCP)

Phencyclidine [1-(1-phyenylcyclohexyl) piperidine] became popular as a general anesthetic in the 1960s, but was rapidly discontinued due to its high incidence of postoperative pychoses and dysphoria. PCP abuse was widespread in the 1970s, waned during the cocaine epidemic in the 1980s, and has recently reemerged in some communities, eg, Los Angeles, as well as some major metropolitan centers in the Northeast.[17]

Pharmacology, Toxicology and Clinical Presentation

PCP is available on the street in a variety of forms: powder, liquid, tablets, leaf mixtures, rock crystal, and as an adulterant in marijuana cigarettes ("illy," "fry," or "hydro"). The effects of PCP are dependent on routes of delivery and dose. Onset is most rapid via the intravenous and inhalational routes, and slowest following oral ingestion. Signs and symptoms of toxicity usually last 4-6 hours, but may last up to 48 hours after large overdose.[18]

PCP is among a group of anesthetics that functionally and electrophysiologically "dissociates" the somatosensory cortex from higher centers. It acts on several receptors in the cortex and limbic structures. PCP blocks N-methyl-D-aspartate receptors and interferes with biogenic amine reuptake.[19] These actions account for its analgesic, anesthetic, cognitive, and psychotic effects, as well as its sympathomimetic and psychomotor effects. PCP at higher concentrations also stimulates the sigma and D2 receptors, which have an inhibitory effect on the cholinergic receptor pathways, leading to sedation, lethargy, and coma.[20]

Phencyclidine users may experience a variety of sensations, including heightened sensitivity to stimuli, dissociation, mood elevation, inebriation, relaxation or tranquilization, hallucinations, increased sociability, and euphoria. Untoward effects include perceptual disturbances, restlessness, disorientation, anxiety, paranoia, hyperexcitability, irritability, mental confusion, and amnesia.[21]

Severe disturbances in vital signs are uncommon in patients who have taken only PCP. Most cases of elevated blood pressure are neither severe nor persistent, but there is a case reported in the literature of hypertensive crisis leading to death following PCP intoxication.[22] Tachycardia has been recorded in up to 30% of patients intoxicated with PCP.[23] Hyperthermia is a relatively rare complication of PCP use, but is a cause of significant morbidity and mortality. There are reports in the literature of PCP-induced malignant hyperthermia causing submassive liver necrosis.[24] Respiratory rate is not significantly different in PCP-intoxicated patients when compared to age-matched, nonintoxicated controls.[25]

Nystagmus, considered one of the hallmarks of PCP toxicity, has been noted in up to 90% of intoxicated patients;[23,25] classically it is described as rotatory, but in actuality it may be in any direction. Early signs of overdose may include miotic pupils, ataxic gait, and increased

Table 4. Drug-Specific Table Of Treatments.

Drug Class	Clinical Presentation	Treatment
Dissociative Agents (PCP, Ketamine)	Agitation	Benzodiazepines
	Hyperthermia	External cooling measures, benzodiazepines
	Rhabdomyolysis	Intravenous hydration, sedation
Hallucinogens (LSD)	Agitation	Benzodiazepines
CNS Stimulants (Cocaine, Amphetamine Analogs)	Agitation	Benzodiazepines
	Hyperthermia	External cooling measures, benzodiazepines
	Rhabdomyolysis	Intravenous hydration, sedation
	Chest pain and myocardial ischemia	Nitroglycerin, benzodiazepines, phentolamine
	Seizures	Benzodiazepines; consider bicarbonate, if cocaine-associated
	Dysrhythmias	ACLS protocol; consider sodium bicarbonate, if cocaine-associated
CNS Depressants (GHB, Opioids)	Respiratory depression	Supportive measures
	Mental status depression	ED observation If known opioid, attempt reversal with naloxone

deep tendon reflexes.[26] Later manifestations of toxicity can include seizures, which in one large series occurred in 3.1% of all patients and 15% of those who were unconscious.[23] Motor signs include dystonic reactions mimicking extrapyramidal effects of neuroleptic drugs, athetosis, catalepsy, posturing, and stereotypies.

Changes in sensorium range from disorientation, lethargy, and stupor to coma.[27] Violence, bizarre behavior, and agitation are the most common behavioral alterations.[23] Other findings include mutism, staring, amnesia, hallucinations, delusions, body image distortion, euphoria, depersonalization, and disordered thought processes.[26,27] While symptoms in adults are mainly psychiatric, PCP intoxication in infants and young children is primarily manifested by neurologic signs, with wide swings in level of consciousness, and a distinctive — although not universal — dull, wide-eyed stare.[28]

More severe cases of overdose can lead to coma of varied duration.[27] Short periods of unresponsiveness are most common, with symptoms of apnea and respiratory depression lasting less than 2 hours. A comatose state can last 2-24 hours, with more severe disturbances in vital signs and autonomic functions, as well as a higher incidence of medical complications. In patients developing prolonged coma, findings on admission may include muscle rigidity, hypersalivation, and hyporeflexia.[27,29]

Rhabdomyolysis and myoglobinuria occur in 2% of PCP-intoxicated patients.[27] Rhabdomyolysis in this population is most likely a result of exaggerated muscle activity,[30,31] which is only exacerbated by the use of restraints without concomitant chemical sedation and may lead to renal failure, if not recognized early and treated appropriately.

Ketamine

Ketamine is a congener of PCP, introduced in the 1970s for use in sedation and anesthesia. It is a dissociative agent, like PCP, but does not produce the same degree of violent, confused behavior. Ketamine was the most widely used battlefield anesthetic in Vietnam, and it is currently the sedative of choice in many pediatric EDs.

Ketamine abuse was first noted on the West coast in the early 1970s in San Francisco and Los Angeles.[21] Later, in the 1980s, there were reports of abuse internationally, though most was confined to medical circles.[32] During the 1990s it was introduced into rave parties and night clubs as an adulterant of MDMA (ecstasy), but quickly gained popularity for its own effects and is now an actively used club drug among young adults.[33,34] Most ketamine used as a recreational drug is diverted from veterinary sources.

Pharmacology, Toxicology and Clinical Presentation

Ketamine is primarily sold in its pure form as tablets, capsules, or powder under the names of "Vitamin K," "Super K," or "Special K." It may be ingested orally, but the usual mode is insufflation of small portions, called "bumps." Oral doses are not well absorbed, but the duration of symptoms can be as long as 4-8 hours.[35] Symptoms after insufflating ketamine typically last 45-90 minutes.

Ketamine users describe floating sensations and dissociation, stimulation, hallucinations, increased cognitive or mental associations, euphoria, and transcendental or religious experiences.[21,36] Sensations are usually described as peaceful, and users are generally not aggressive. One unique experience, feared by ketamine users, is the "K-hole," a dysphoric dissociated state that can sometimes reproduce the features of a near-death experience.[36]

Ketamine users may complain of anxiety, chest pain, and palpitations.[37] Other noxious side effects include ataxia, dizziness, slurring of speech, hyperexcitability, unpleasant imagery, vomiting, confusion, and unresponsiveness.[21,38] Because ketamine has a short duration of action, up to half of those who seek care have no complaints by the time they present to the ED.[37] Some recreational users, however, may display residual effects up to 3 days after ingestion, including semantic memory impairment and dissociative and schizotypal symptomatology.[39,40]

Ketamine use should be suspected in any patient presenting with agitation, tachycardia, and either visual hallucinations or nystagmus, although the absence of any of these does not rule out this diagnosis. Physical examination findings are nonspecific. Nystagmus is seen in only 15% of patients. Altered mental status with hallucinations, unresponsive, "trance-like" states,[38] and combativeness are commonly found in ketamine-intoxicated patients.[37] Other reported findings include mydriasis, slurred speech, and hypertension.

Mild cases of rhabdomyolysis have been noted in patients who were combative and required benzodiazepines for sedation.[37] There is 1 case reported in the literature of dystonic reaction occurring after ketamine abuse,[41] and 2 cases of ketamine-associated pulmonary edema.[42,43] Both cases involved ketamine use as an anesthetic agent at doses higher than those self-administered by recreational users, and both patients recovered without complications. Most ketamine-associated deaths reported in the literature thus far have been mixed-drug fatalities.[44,45] One case of an autoerotic accident involving a fatal combination of asphyxia by suffocation and intoxication in which toxicological analysis found only ketamine has been reported.[46]

Treatment of Dissociative Agent Toxicity

Management of dissociative agent toxicity is primarily supportive. PCP and ketamine may produce severe agitation that requires chemical sedation. Several articles have been published supporting the use of antipsychotics for sedation.[8,47] However, antipsychotics are best avoided in any patient with unstable vital signs, since they can interfere with heat dissipation and may induce either seizures or dysrhythmias. The agitation, hypertension, and/or tachycardia seen with dissociative agents are best treated initially with benzodiazepines, eg, diazepam, 5-10 mg IV, or lorazepam, 2-4 mg IV.[37,48] Benzodiazepines may relieve myotonic and hyperkinetic thermogenesis. Hyperthermia, when severe, is aggressively treated with external cooling measures, while rhabdomyolysis, when present, is treated

with fluid resuscitation and possibly urinary alkalinization.[49]

Hallucinogens

LSD

In 1943, while searching for a new analeptic agent, Albert Hoffman was exposed to d-lysergic acid diethylamide (LSD), a semisynthetic derivative of lysergic acid, and noted "kaleidoscope-like" hallucinations.[50] LSD was used therapeutically for some time in the 1950s as a psychiatric drug and as an experimental model for schizophrenia.[51] It became popular with American college students in the 1960s, its use famously advocated by such cult figures as Timothy Leary.[50] In 1966, a federal law banned the use of LSD, due to public health concerns. While its popularity diminished in the late 1970s and early 1980s, in the 1990s its use steadily increased. The vast majority of users are middle-class adolescents and young adults. LSD continues to be a popular drug at major rock concerts[52] and has become more popular in the rave scene.[53]

Pharmacology, Toxicology and Clinical Presentation

LSD is distributed primarily in the form of squares of blotter paper saturated with the liquid. It can also be found in liquid form in breath mint bottles and vials, in gelatin tabs, or in a pill form known as a "microdot."[53] The strength of LSD samples currently obtained from illicit sources ranges from 20 to 80 micrograms of LSD per dose. This is considerably less than the levels reported during the 1960s and early 1970s, when the dosage ranged from 100 to 200 micrograms, or even higher, per unit.

LSD is well absorbed with a peak effect usually within 2-4 hours and lasting 6-12 hours.[51] LSD and many other hallucinogens are structurally similar to serotonin (5-HT) and appear to produce their effects by binding to and activating 5-HT2 receptors.[54,55]

Within minutes of ingestion, dizziness, weakness, paresthesias, blurred vision, chilliness, headache, and nausea may occur. Users can also develop ataxia and tremor. In the second or third hour, visual illusions and hallucinations usually appear; there may be synesthesias (a melding of the senses, such as "hearing" colors or "seeing" sounds), altered body image, depersonalization, and derealization, which may precede the hallucinogenic effects.[50] People experiencing these effects are usually fully awake, alert, and oriented, and they generally realize they are under the influence of a drug.

Signs and symptoms are dose-related and associated with the user's degree of tolerance.[51] Tolerance does develop rapidly, and there is cross-tolerance of LSD with other hallucinogens, such as mescaline and psilocybin. Response to LSD varies, even in the same individual at different times.[56] Patients may experience either euphoria or agitation, depending on the setting and personality of the individual. There is no physiologic dependence syndrome reported with LSD use. LSD intoxication may be difficult to diagnose when only part of the history is available. Synesthesias are pathognomonic of hallucinogen ingestion, and if these are elicited in the history, the diagnosis of LSD intoxication is more likely.

Patients experiencing a "bad trip" secondary to acute LSD intoxication may present to the ED with panic reactions, psychosis, and major depressive dysphoric reactions. These can lead to suicide or homicide attempts and unintentional deaths associated with perceptual distortions. Patients may also present with mydriasis, tachycardia, hypertension, tachypnea, hyperthermia, and diaphoresis. These sympathetic effects do not stem directly from the chemical action of LSD; rather, they are physiologic responses to the experience.[51] Very high doses of LSD may produce hyperthermia, coma, and/or respiratory arrest.[57,58] Other complications reported with severe LSD intoxication include rhabdomyolysis and myoglobinuric renal failure, hepatic necrosis, and disseminated intravascular coagulation secondary to hyperthermia. These complications are extremely rare and most patients never present for medical care after using this drug.

Long-term reported consequences of LSD use include prolonged psychotic reactions, depression, and exacerbation of psychiatric illness. Some patients may present to the ED with spontaneous recurrence of LSD symptoms, without having taken the drug. This is known as hallucinogen persisting perception disorder (HPPD), or "flashbacks." Flashbacks diminish in duration, frequency, and intensity over months or years.

Treatment of the Patient with Hallucinogen Toxicity

Hallucinogens rarely produce life-threatening problems. Toxicity from these agents is best treated by making the patient feel secure and cared for in a quiet, calm environment. If sedation is needed, any of the benzodiazepines can be used. The patient with HPPD rarely presents to the ED. Anecdotal reports suggest that HPPD may be treated with benzodiazepines,[50] though SSRIs or naltrexone[59-61] have also been reported to be effective.

CNS Stimulants

Cocaine

Cocaine is a naturally derived CNS stimulant extracted and refined from the coca plant (*Erythroxylon coca*), which is grown primarily in the Andean region of South America. In ancient times South American natives used coca for both religious and medicinal purposes. They used its stimulant properties to fight fatigue and hunger, and to enhance endurance. In 1886, cocaine became the major active ingredient in Coca-Cola® in its original formulation.[62] In the early 1900s, the first cases of nasal damage from cocaine were reported in the literature. Soon thereafter, President Woodrow Wilson signed a law making cocaine a prescription medication. By 1924, a report of 26 deaths attributed to cocaine was published.[63]As reports on the adverse effects of cocaine mounted, Coca-Cola® became completely cocaine-free in 1929. Today, cocaine has very few therapeutic indications, and its importance derives

from being considered an abusable drug.

The societal, medical, and financial costs of cocaine abuse are staggering. A chart review of 14,843 NYC residents 15-44 years of age from 1990-1992 demonstrated that 1 in 4 residents who received fatal injuries was a recent cocaine user, and that 18.3% tested positive for cocaine at autopsy.[64] One third of deaths after cocaine use in this study were the direct result of drug intoxication. In 2003, approximately 1 in 5 drug-related ED visits, or 126,000 visits in the USA, involved cocaine.[65] Chest pain is the most frequent cause for ED visits following cocaine use[66] and costs an estimated $80 million.[67]

Pharmacology, Toxicology and Clinical Presentation

Cocaine is self-administered by a number of different routes: oral, intranasal, intravenous, and via smoking. The most common method of cocaine use is "snorting" or inhaling the drug in its hydrochloride form. The user experiences 20-40 minutes of stimulation after inhalation. Cocaine "free base," or "crack," in which the cocaine alkaloid is "freed" from its hydrochloride form, is the second most popular form and produces a high for 10-20 minutes.[68] Circulating cocaine is hydrolyzed primarily by plasma pseudocholinesterase or liver esterases to benzoylecgonine and other minor metabolites, which are then excreted into the urine.[69] Urinary benzoylecgonine can be detected up to 72 hours after recreational cocaine use, but chronic cocaine users may have a positive urinary metabolite test up to 3 weeks after final cocaine consumption.[70]

Cocaine has 2 distinct physiologic effects: it is a local anesthetic as well as a monoamine reuptake inhibitor.[71] Cocaine binds within the Na^+ channel, inhibits Na^+ conduction, and blocks ion conduction within electrically active myocardial and nerve cells. Cocaine's inhibition of monoamine reuptake systems results in enhanced actions of norepinephrine, epinephrine, and dopamine.[71]

Cocaine users experience euphoria, increased sexual stimulation, increased energy, and decreased fatigue and appetite. A biphasic response is often observed, beginning with a stimulant effect, followed 30-60 minutes later with a "crashing" effect characterized by feelings of depression, anxiety, fatigue, and desire for more cocaine.[72] Other adverse effects reported include insomnia, irritability, and personality changes.[73] Cocaine may produce a myriad of clinical manifestations, including vital sign abnormalities, neurological symptoms, cardiac effects, pulmonary effects, and other vascular catastrophes.

Hyperthermia from cocaine use is likely due to a combination of increased heat generation and a decreased ability to dissipate heat, due to vasoconstriction of blood vessels within the skin.[74] High ambient temperature is associated with a significant increase in mortality from cocaine use.[75] This association is most likely due to the combined effect of hot weather taxing cardiovascular function and cocaine-induced thermogenesis and sympathetic overdrive.

Hypertension, tachycardia, coronary artery vasospasm, and increased myocardial oxygen demand are expected in the setting of cocaine intoxication, because of the alpha-adrenergic and beta-adrenergic effects of the drug. Conduction disturbances are in large part the result of sodium channel blocking or "quinidine-like" effects, which may manifest as prolonged QRS, QT, and QTc intervals. Arrhythmias, such as sustained ventricular tachycardia or ventricular fibrillation, usually occur in the setting of cocaine-associated myocardial infarction.[71] Cardiac ischemia results from increased coronary vascular resistance, focal coronary vasospasm (especially at sites of preexisting coronary stenosis), enhanced platelet aggregation, and increased myocardial workload.[71]

Consider the possibility of other vascular catastrophes in patients who present with chest pain or abdominal pain after cocaine use. One retrospective chart review of patients with acute aortic dissection found that 37% of cases were related to cocaine use. The mean interval between cocaine use and onset of symptoms was 12 hours.[76] Cocaine has also been implicated in acute coronary-artery dissection and consequent myocardial ischemia.[77] Numerous cases of mesenteric ischemia in patients without previous history of atherosclerosis have been reported in cocaine users.[78] These patients may present to the ED with an acute surgical abdomen due to bowel perforation.[79]

Cocaine-mediated vasoconstriction produces a significant decrease of relative cerebral blood flow,[80] and this may account for cocaine's association with cerebral infarction. Cocaine is also a significant risk factor of nontraumatic intracranial hemorrhages, according to several autopsy studies.[81,82] Seizure threshold is reduced in patients with underlying epilepsy, or cocaine may be the only provocative factor in patients presenting with a seizure to the ED.[83] Cocaine-related seizures most frequently are single, generalized, and will not demonstrate abnormalities on CT or EEG. Subjects presenting with focal or multiple seizures often have underlying intracranial hemorrhage or ischemic stroke.[84]

Cocaine abuse can lead to a variety of pulmonary complications. Barotrauma (pneumomediastinum, pneumothorax, and pneumopericardium)[85,86] and bullous emphysema[87] are commonly related to cocaine inhalation in the free-base or crack form and occur as a result of coughing or intense Valsalva maneuver performed to heighten the effect of the drug. Pulmonary edema[88] has been described, especially after crack use, and is thought to be the result of increased capillary endothelial permeability and increased protein concentration. Other pulmonary complications include bronchospasm,[89] alveolar hemorrhage,[90,91] pneumonitis,[92] bronchiolitis obliterans,[93] vasculitis,[94] and pulmonary hypertension.[95]

Amphetamine and Analogs

Amphetamine (alpha-methyl-phenylethylamine) was first synthesized in 1887 in Germany, but nothing was done with the drug until the late 1920s, when it was seriously investigated as a cure or treatment for a variety of illnesses. The subsequent popularity of amphetamine led to the creation of several analogs. Methamphetamine, more potent and easier to make than amphetamine, was discovered in Japan in 1919, and MDMA (3-4 methylene-

dioxymethamphetamine) was discovered in Germany in 1913. During World War II, soldiers used amphetamines to combat fatigue and enhance performance. Following the war, methamphetamine tablets were vigorously promoted by pharmaceutical companies. Epidemic intravenous use of the drug soon followed.[96] Large quantities of amphetamines were sold by drug companies during the 1950s to college students, athletes, truckers, and housewives, as well as thousands of veterans returning from the war with amphetamine habits. Subsequent control in Schedule II of the Controlled Substances Act (CSA) in 1970 placed restrictions on, among other things, the amounts of these drugs produced. Today, most amphetamines distributed to the black market are produced in clandestine laboratories. In the 1980s, MDMA gained popularity as a drug of abuse, resulting finally in its placement in Schedule I of the CSA.[97] Mood-modifying amphetamines, such as MDMA ("Ecstasy" or the "love drug"), MDA (3,4 methylenedioxyamphetamine, or "Adam"), MDEA (3,4-methylenedioxethamphetamine, known as "Eve"), and MDMB (methylbenzodiolbutanamine), have recently obtained reputations as dance drugs and are often all sold as "ecstasy."

Pharmacology, Toxicology and Clinical Presentation

Amphetamines as a class share a remarkable structural similarity to the naturally occurring catecholamines. Amphetamine, the prototypical agent and the drug after which the class is named, acts both directly and indirectly to release endogenous catecholamines, especially norepinephrine and dopamine.[98] The release of catecholamines leads to stimulation of both central and peripheral alpha- and beta-adrenergic receptors. Methamphetamine and "ecstasy" are modified amphetamines that are more centrally acting and/or lead to a greater increase in central serotonergic tone than amphetamine. Amphetamines are metabolized in the liver via the cytochrome p450 system, and important drug interactions have been reported. CYP2D6 inhibitors, such as ritonavir, may elevate blood levels of MDMA, which is also metabolized by the CYP2D6 isoenzyme.[99]

Users of amphetamines report acute effects that include euphoria, increased physical and emotional energy, heightened sexual awareness, and decreased appetite. Symptoms may include gait instability, trismus, and decreased motivation to perform mental or physical tasks.[100] Agitation is common, and psychosis (likely due to increased central dopaminergic tone) is well reported. The predictable clinical result of increased catecholamine tone is overactivity of the sympathetic nervous system. Intoxication with amphetamines manifests as a sympathomimetic toxidrome, including mydriasis, agitation, tachycardia, and hypertension.

Hyperthermia has been recognized as a prominent feature in fatal amphetamine poisonings for 3 decades. One study in Ontario published in 1975 suggests that hyperthermia contributes to a significant percentage of deaths — 12 out of 26 fatalities during the study period.[101] Elevation in body temperature is likely the result of 2

Cost- And Time-Effective Strategies For Treating Substance Abuse And Acute Overdose In The ED

1. Consider ED discharge and/or psychiatric clearance at 4 to 6 hours, if no consequences of the abuse/OD have medically manifested and levels of dangerous ingestants (aspirin, acetaminophen, etc) are zero.

While not well studied at this time, most experts agree that at 4 and certainly at 6 hours a serious medical complication will arise and manifest if the overdose was not in large quantities, was mixed, or was unknown. Of course, the patient should be alert and oriented, with normal vitals signs and normal gait, to be deemed ready for discharge.

2. Consider starting a naloxone drip early, if an opioid overdose involved a long-acting agent, such as methadone.

Starting the drip early and titrating it properly will keep the patient oxygenating and ventilating within normal limits, while allowing yourself and the nursing staff a little "breathing room" to move onto other things in the ED. Continued necessity of the naloxone drip to maintain ventilation should prompt admission to the hospital.

3. Refer substance abuse patients for detoxification and therapy at certified alcohol and drug treatment centers.

The manifestations of substance abuse — including death to loved ones, injury and trauma, permanent disability, domestic and child abuse, divorce and job-related issues (including unemployment) — cost countries and its taxpayers billions of dollars per year. Putting someone back on the right track, helping to move them away from substance abuse, may be the best treatment a patient can be prescribed.

4. Patients with chest pain in the setting of CNS stimulant use (cocaine or amphetamine analogs) can be safely discharged after 12 hours if they are pain-free, have normal serial cardiac enzymes and ECGs, and have no other risk factors for myocardial ischemia.

If patients have no cardiovascular complications during a 9-12 hour observation period after stimulant-induced chest pain , they have a very low risk of death or myocardial infarction in the 30 days after discharge.

5. Sedate agitated patients early to avoid complications from rhabdomyolysis.

Patients who are physically restrained are at high risk for rhabdomyolysis leading to acute renal failure. Avoid this complication by sedating them with a benzodiazepine, keeping them in a quiet area of the ED, and providing gentle intravenous hydration, if needed. ▲

synergistic mechanisms: increased dopaminergic neurotransmission leading to increased body core temperature[102] and sympathetically mediated peripheral vasoconstriction reducing heat release.[103] The hyperthermic effect of these drugs, together with the intense physical activity of energetic dancing or agitation, leads to exertional rhabdomyolysis[104-106] and can result in rapid elevation of serum CPK and acute renal failure. More severe cases of hyperthermia can lead to liver failure manifesting as jaundice and hepatomegaly and disseminated intravascular coagulation.[106,107]

Life-threatening and fatal hyponatremic complications following ecstasy use are well documented in the literature. Patients presenting with vomiting and disturbed behavior, drowsiness, mute state, and seizures may be suffering from this unique toxicity of the popular club drug.[108] MDMA-induced hyponatremia is the result of inappropriate secretion of antidiuretic hormone[109,110] combined with excessive water intake.[111]

Amphetamine-associated myocardial ischemia is likely a result of vasospasm, thrombus formation, increased oxygen demand, and direct myocardial toxicity — mechanisms similar to cocaine.[112-115] In one retrospective chart review of patients presenting with chest pain after methamphetamine use, 25% of patients were diagnosed with acute coronary syndrome.[114] Cardiac irritability, including ventricular and supraventricular arrhythmias, may follow amphetamine use[114,115] and are not necessarily associated with acute ischemia.[114] Always keep a broad differential in mind when patients present with chest pain. Amphetamines have been implicated in cases of coronary artery rupture and acute aortic dissection.[116-119] Other cardiovascular complications associated with amphetamine use include both ischemic and hemorrhagic cerebrovascular accidents, which manifest as seizures or focal neurologic deficits.[120-122]

Treatment of CNS Stimulant Toxicity

The management of the stimulant-intoxicated patient depends a great deal on the symptoms with which the patient presents. A patient with mild agitation may need no more than treatment with benzodiazepines and observation for several hours, while a patient with a cocaine-induced myocardial infarction may require intensive pharmacotherapy and percutaneous coronary intervention.

Cardiopulmonary resuscitation is the first priority in patients presenting with apnea, dysrhythmia, or cardiac arrest. Treatment of psychostimulant-induced dysrhythmias generally follows ACLS guidelines. In addition, some case reports and results from several animal studies have demonstrated sodium bicarbonate (1-2 mEq/kg IV push) can reverse wide-complex rhythms in the setting of cocaine use.[123,124]

Furthermore, seizures or severe agitation deserve prompt treatment for airway protection and to prevent their contribution to further complications, such as hyperthermia and rhabdomyolysis. Benzodiazepines are first-line for sedation and treatment of seizures. Theoretically, like tricyclic antidepressant-induced seizures, cocaine-induced seizures may respond to sodium bicarbonate injection.

If psychostimulant-intoxicated patients do not succumb to cardiac or cerebrovascular events, controlling hyperthermia and treating rhabdomyolysis are the most significant steps in preventing further morbidity. Always maintain a high index of suspicion for hyperthermia in the setting of pscyhostimulant abuse. Aggressive cooling measures, if instituted immediately, can lead to successful outcomes.[125,126] While antipsychotic agents may seem attractive,[127] they should not be used in patients with (or at risk of developing) hyperthermia, since they interfere with heat dissipation via their anticholinergic effects. Benzodiazepines should be used early; in more severe cases, consider paralysis and mechanical ventilation.[128]

The hypertension and tachycardia seen after psychostimulant abuse is in part centrally mediated, so centrally acting sedatives (eg, benzodiazepines) are often sufficient treatment. Beta-blockers may exacerbate hypertension through unopposed alpha-adrenergic activity and should be avoided.[129,130] Labetalol, a beta-antagonist with weak alpha-antagonist properties, effectively reduces the pressor response to psychostimulants.[131] However, labetalol has been shown to increase mortality in animal models, and thus its use is generally discouraged.[132] In the event that the blood pressure does not improve with benzodiazepines, nitroprusside, nitroglycerin, or phentolamine can be administered (see below).

A single electrocardiogram (ECG) is insufficient to exclude psychostimulant-induced myocardial ischemia.[133] In one study, young cocaine–chest-pain patients who do not have evidence of ischemia or cardiovascular complications over a 9 to 12 hour observation period have a very low risk of death or myocardial infarction in the 30 days after discharge.[134] In this 302-patient cohort, none of the patients died of a cardiovascular event during the 30-day follow-up period. Low-risk patients who may be discharged are those with normal serial troponin I levels, nonischemic ECGs, and no cardiovascular complications, such as dysrhythmias, hypotension, or recurrent symptoms.[134] Because amphetamine-induced chest pain and myocardial ischemia are likely due to similar mechanisms as cocaine, we suggest the same ED management.

Treatment of ECG-confirmed, psychostimulant-induced myocardial ischemia or infarction begins with oxgygen, benzodiazepines (to control agitation and treat centrally mediated hyptertension and tachycardia), and aspirin. Nitroglycerin is effective in this setting and may be used both as an agent to treat pain and for blood pressure control, if necessary.[135-137] Alpha-adrenergic receptors are critical for many of the hemodynamic responses of stimulants, and alpha-blockers have been shown to blunt the arterial pressure, heart rate, and vasoconstrictor responses to cocaine in animals.[138] Phentolamine (up to 5 mg IV in 1 mg increments) may be useful in alleviating chest pain not responsive to the conventional medical

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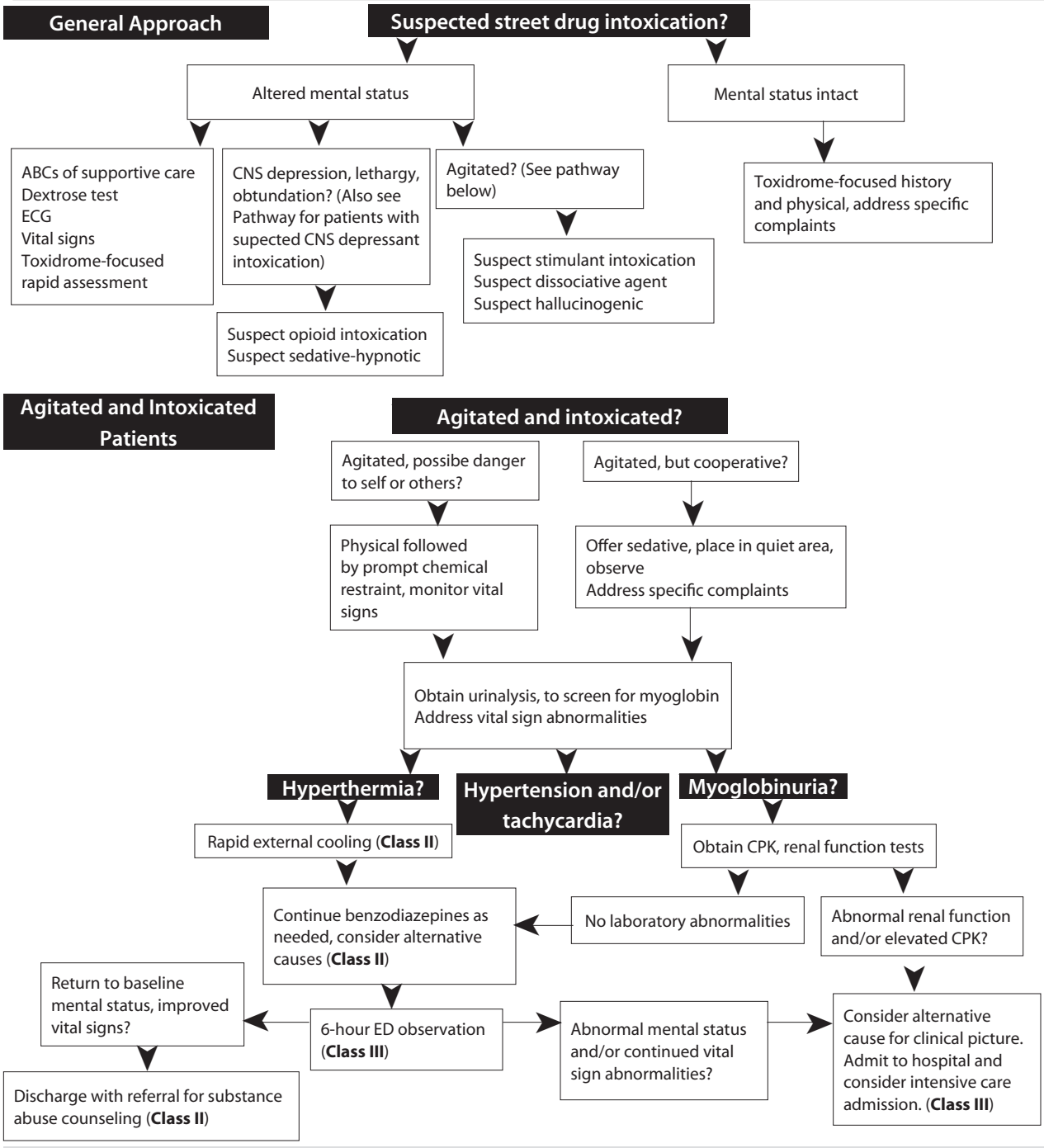
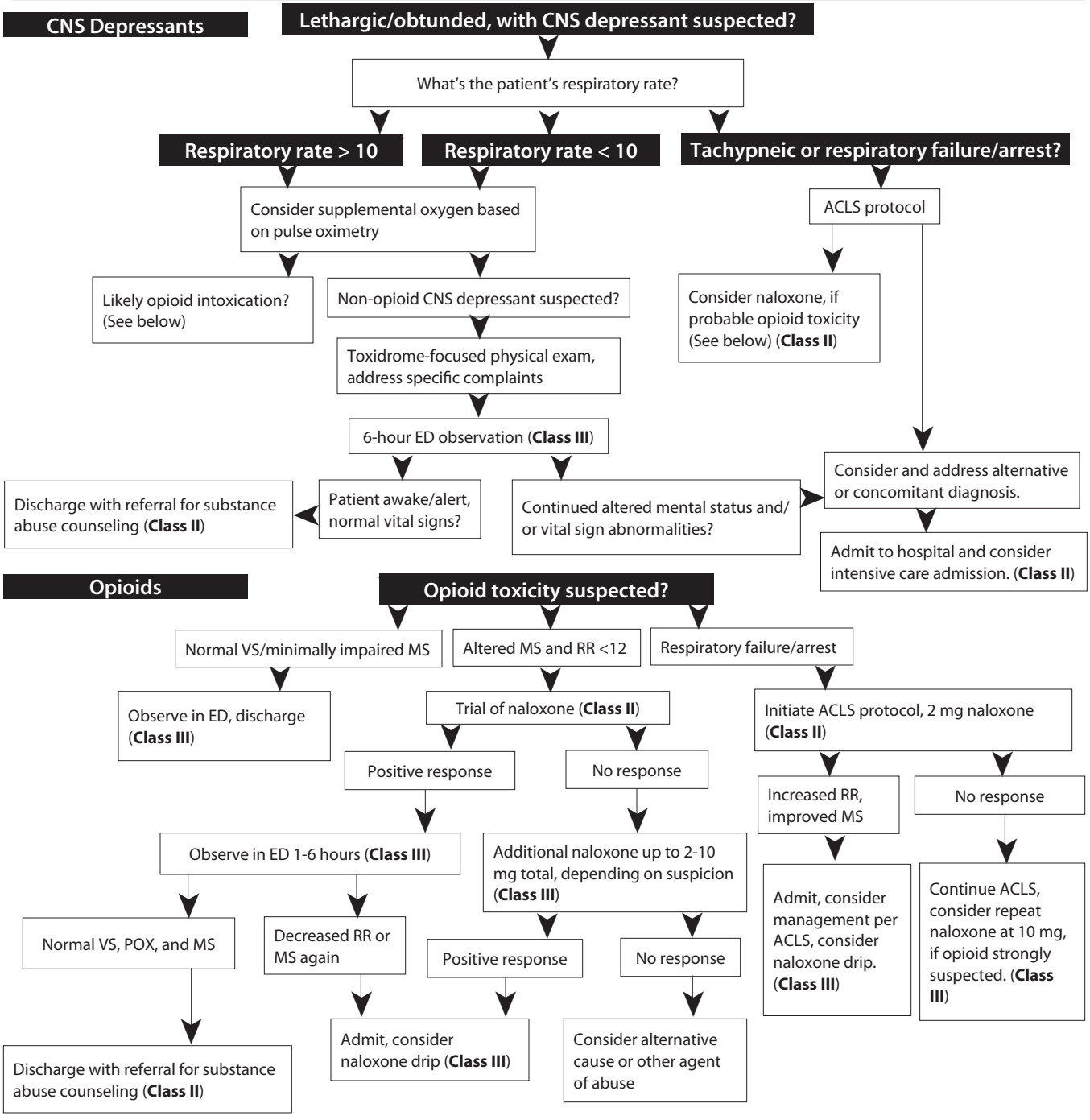
Clinical Pathways: General Approach To Intoxicated Patients And Management Of Intoxicated And Agitated Patients



The **evidence for recommendations** is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair-to-good evidence provides support. **Indeterminate:** Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Clinical Pathways: Lethargic Or Obtunded Patients With Suspected Intoxication And Treatment Of Opioid Toxicity



The **evidence for recommendations** is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair-to-good evidence provides support. **Indeterminate:** Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Continued from page 10

management.[139,140] Patients with persistent chest pain and ECG abnormalities should be considered for thrombolytic therapy or emergency cardiac catheterization, as underlying coronary artery thrombosis cannot be excluded.[113,114,141]

Although there is not much evidence reported in the literature, in theory other complications of stimulant abuse, such as ischemic stroke and mesenteric ischemia, may improve when vasospasm is reversed with a trial of phentolamine. Prompt surgical consultation in all cases of mesenteric ischemia is warranted. The use of thrombolytic agents in these settings has not been studied and would require a careful risk-benefit analysis before using them. Hemorrhagic stroke is treated in the same manner as hemorrhagic stroke from other causes, except that beta-blocking agents (such as esmolol or labetalol) should not be used to control hypertension.

Thoracic aortic dissection is a known complication of stimulant use, and management is similar for patients with aortic dissection from other causes, with the exception that beta-adrenergic antagonists should not be used for the reasons outlined above. Always consider and rule out aortic dissection in any patient presenting with chest pain, as thrombolytic therapy may be a cause for their demise. Barotrauma should be identified and managed early, with tube thoracostomy and/or surgical intervention, if necessary.

In patients with MDMA-associated hyponatremia, initial treatment depends on volume status. If the patient is dehydrated on clinical examination, careful volume resuscitation with a crystalloid, such as 0.9% sodium chloride, is indicated to achieve euvolemia. Euvolemic patients presenting with seizures or altered mental status due to hyponatremia should receive hypertonic saline, with the goal of raising the serum sodium at an hourly rate of 1-2 mmol/L.[142] Correction faster than this may result in central pontine myelinolysis. Once profound volume depletion is addressed and hypertonic saline is administered, when needed, fluid restriction is the treatment of choice.

CNS Depressants

GHB

Gamma-hydroxybutyrate (GHB) was first synthesized and introduced into clinical medicine in the 1960s as an anesthetic agent. It is still used in Europe as both an anesthetic and in the treatment of alcohol withdrawal. Within the US, the only FDA-approved use is limited to narcolepsy treatment.[143] In 1977, Japanese investigators reported that GHB had steroid-enhancing effects. GHB became popular with bodybuilders in the 1980s and was advertised as an agent that could increase muscle development and burn fat, as well as increase libido. As GHB's popularity increased in the 1990s, its ability to induce euphoria became evident, and it grew popular at "rave" parties and as a "date rape" drug.[144] In early 2000, GHB was reclassified as a Schedule I controlled substance. Since then, its chemical precursors — gamma-butyrolactone (GBL) and 1,4 butanediol (1,4 BD) — have become popular sources of the drug. Both are converted in vivo by endogenous enzymes into GHB. Gamma-valerolactone 4-pentanolide (GVL) is frequently abused in place of GHB, as it is metabolized into gamma-hydroxyvalerate methyl-GHB (GHV), which produces physiologic effects similar to GHB. These GHB analogs are principally found in chemical solvents.[145]

Pharmacology, Toxicology and Clinical Presentation

Gamma-hydroxybutyrate is a naturally occurring fatty acid derivative of the major CNS inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). The exact role of endogenous GHB is unknown, but it may have effects on sleep cycles, body temperature, cerebral glucose metabolism, and memory.[144] GHB acutely impairs dopaminergic transmission, probably via an action on a unique GHB receptor, or on $GABA_B$ receptors.[146,147] There is also evidence of increased acetylcholine and 5-hydroxytryptamine levels after administration of GHB, and GHB may interact with CNS opioids.[147] These GHBergic and GABAergic potentiations induce a short-lived sedative action.

GHB's lipophilic properties allow for its rapid absorption by the gastrointestinal tract and its ability to cross the blood-brain barrier. Onset of symptoms following oral ingestion of GHB is generally within 15-30 minutes,[148] and its half-life is only 20 minutes.[144] Onset is delayed after ingestion of GBL or 1,4 BD.

Vital sign abnormalities are common after GHB intoxication. Bradycardia is reported in up to 36% of GHB-intoxicated patients presenting to the ED[149-151] and appears to be associated with lower GCS scores.[149] Respiratory depression is often a significant component of acute GHB intoxication. Patients may present with a decreased respiratory rate, prolonged apneic periods, agonal respirations, or complete apnea requiring endotracheal intubation.[150,152,153] One large case series reported an 11% incidence of hypotension; all of these cases, however, involved coingestion of GHB with alcohol and/or another drug.[149] Mild hypothermia has also been reported.[149]

GHB-intoxicated patients most commonly present to the ED with CNS depression. In the largest case series of GHB overdose, 28% of cases had a GCS score of 3, and 33% had scores ranging from 4 through 8.[149] Awake patients may present with confusion, pressured speech, and ebullience, or they may be combative.[152] Patients with GHB intoxication may alternate between episodes of profound unconsciousness and marked agitation.[153] Other than coma, neurologic events are relatively uncommon, but may include weakness, incontinence, hallucinations, incoordination, dizziness, and temporary amnesia.[150,152] Case reports and case series have suggested that GHB intoxication results in seizure-like activity.[149-151,153,154] Anesthetic induction with GHB is frequently associated with random clonic movements of the face and extremities, although these are not associated with epileptiform EEG changes.[153]

Gastrointestinal symptoms are common in GHB-intoxicated patients. Emesis is seen most frequently, with an

incidence between 14-44%.[150,153] Nausea without vomiting and diarrhea has also been reported.[152] One case series found that emesis was observed most commonly during the final emergence from consciousness. However, several cases involved vomiting during fluctuating levels of consciousness.[149]

Pulmonary edema is infrequently reported after ingestion of GHB or congeners.[155,156] There are reports of ECG changes associated with GHB, including U waves, first-degree AV block, atrial fibrillation, and right bundle branch block; all patients had ingested other drugs, however, and no old ECGs were available for comparison, thus preventing any conclusions.[149,153,157]

The majority of patients presenting with GHB intoxication will have no remarkable abnormalities on electrolyte levels or blood counts.[149,153] GHB is not included in standard drug screens, but it can be detected in the urine or serum by gas chromatography, colorimetry, and mass spectrometry.[158-160]

Severe GHB dependence develops after prolonged, frequent ingestion. Onset of withdrawal symptoms may be rapid, occurring within 1 to 6 hours after the last dose.[161] The GHB withdrawal syndrome is similar to that of other sedative-hypnotics, with early symptoms of insomnia, tremor, confusion, nausea, and vomiting. Patients may not seek medical care until the more severe symptoms of agitation and hallucinations develop, typically after 1 day of abstinence. Untreated, the withdrawal syndrome progresses over the initial 2-3 days, with autonomic instability manifested by tachycardia, hypertension, tremor, and diaphoresis.[161,162] Confusion, disorientation, and delirium with agitation and combative behavior develop as the syndrome progresses, often necessitating the use of restraints and sedation. Like alcohol withdrawal, GHB withdrawal is a medical emergency, and at least 1 death has been reported.[161]

Treatment of GHB Toxicity

Despite the dramatic presentation of coma and respiratory depression in GHB-intoxicated and overdose patients, those who present to the ED have excellent outcomes. In a large case series of reported GHB intoxication, 87 out of 88 patients were discharged within 24 hours of presentation, and the other was admitted to a psychiatry ward for suicidal ideation.[149] Confirmed deaths directly attributable to GHB, due to cardiorespiratory depression and loss of airway, have thus far occurred only outside the hospital setting.[163] There are no reports in the literature of fatalities after seeking medical attention. Patients usually recover full respiratory and CNS functions within the first 6 hours of presentation, although time to recovery is dependent on GCS on arrival. One case series reported mean recovery time for GCS scores between 9 and 13 at 116 minutes (range, 16-260); for those with an initial GCS between 3 and 5, the mean recovery time was 177 minutes (range, 31-389).[149] Because of the rapid recovery from GHB intoxication, most patients can be discharged home from the ED after a period of observation.

Most cases of GHB intoxication do well with supportive measures. Although a routine dictum in the ED is that trauma patients with a GCS of 7 or less should be intubated, this may not hold true in the setting of GHB intoxication. In one case series, 17 out of 25 patients with a GCS of 3 were not intubated, yet all were discharged within 24 hours.[149] It should be stressed, however, that a published case series cannot substitute for clinical judgement, and the decision to intubate must be made at the bedside of each patient. Bradycardia is usually transient, and responds to atropine.[149,164] Hypotension should be treated with intravenous fluids; vasopressors are rarely, if ever, necessary.

Management of GHB withdrawal is symptomatic and supportive. Benzodiazepines were used successfully in 1 case series to achieve sedation, although extremely high doses were necessary in some patients.[161] Severe withdrawal resistant to benzodiazepine therapy was treated with pentobarbital in 1 case series, resulting in excellent control of behavioral, autonomic, and psychiatric symptoms.[162] Propofol is likely to be as useful as pentobarbital in refractory GHB withdrawal, and it may be a better choice, in that most ED and ICU staffs have greater familiarity and comfort using it.

Opioids

The naturally occurring opiates — codeine and morphine — are found in the opium poppy, *Papaver somniferum*, and its use is recorded as early as 1500 BC. Dozens of other synthetic and semisynthetic opioids have entered into medicinal and recreational use and abuse since that time. Opioid (ie, narcotic) abuse continues in epidemic numbers in the United States and touches nearly every region of the world. ED visits for heroin abuse doubled in the US between 1993 and 1996, with the annual rate remaining steady since then.[165] Opiate exposures lead to a disproportionately high number of deaths, relative to all toxicities in general, as reported by US poison control centers and medical examiners' offices.[166] In people who regularly inject heroin, the average annual mortality rate is 2%; half of this rate is attributable to overdose. Most heroin-related deaths occur in the company of other people, and medical attention generally is not sought until it is too late.[167] Most deaths occur among users who are in their late 20s to early 30s.[165]

Pharmacology, Toxicology and Clinical Presentation

Opioids may be inhaled, injected intravenously, insufflated, ingested orally, or applied transdermally. Peak effects vary depending on the route of ingestion. Opioids act on multiple receptors, designated as mu, kappa, and delta in one nomenclature scheme, and OP1, OP2, and OP3 in another.

Opioids produce euphoria, which accounts for their abuse potential. They also produce miotic pupils, an effect reflecting the mediated excitation of the parasympathetic nerve innervating the pupil.[165] There are some exceptions

to the rule that opioids produce miosis, including meperidine, pentazocine, propoxyphene, and the combination of diphenoxylante and atropine. Respiratory depression is associated with all opiates, and occurs as a direct effect on the respiratory centers of the brainstem that lead to decreased responsiveness to carbon dioxide, which leads in turn to a diminished respiratory rate. Opiates also decrease gut motility.

Opioids are metabolized by hepatic conjugation to inactive compounds and excreted in the urine. Many opiates, such as heroin, undergo extensive first-pass metabolism and are thus poorly effective by the oral route, but still life threatening after massive ingestion (see Special Circumstances, Body Packers and Body Stuffers, on page 17). Hepatic insufficiency will delay the metabolism of opioids and prolong their half-lives.

Treatment of Opioid Toxicity

Patients who are obtunded, with constricted pupils and a markedly decreased respiratory rate, are likely opioid

Ten Pitfalls To Avoid

1. "The patient had chest pain and ECG changes, so we gave him a beta-blocker. We didn't think to ask about cocaine use."

Physicians must recognize that a common cause of chest pain in young adults is cocaine use. Use of beta-blockers may lead to a hypertensive crisis through unopposed alpha-adrenergic activity.

2. "The urine dipstick was negative and the patient was uncooperative, so I thought it was okay not to start an IV."

The absence of myoglobin on a urine dipstick test does not rule out rhabdomyolysis. The time from ingestion of drugs to presentation to the ED may be insufficient for renal clearance of plasma myoglobin, especially in the patient who has excess muscle activity due to agitation or seizures.

3. "The patient just would not cooperate, so I gave him some Haldol® before the nurse got his vital signs."

Haloperidol should not be administered to combative, drug-intoxicated patients without initial assessment of vital signs, especially in the setting of hyperthermia.

4. "I gave him Narcan® just a couple of hours prior. I didn't know he'd have a respiratory arrest again."

Naloxone has a short half-life and clinical effect. If the patient is under the influence of a large overdose or a long-acting opioid, large doses and/or frequent redosing of naloxone may be necessary. A naloxone drip, run at a dosage that gives enough of a clinical effect (alertness without respiratory depression, but without overt withdrawl symptoms), should be used if the clinician anticipates frequent redosing of naloxone may be necessary.

5. "No one could get a line in her for naloxone, so we had to intubate her — we couldn't keep bagging her."

Naloxone may be given intramuscularly, subcutaneously, endotracheally (down the ET tube), and even sublingually, though hypoperfusion may slow its effect if given IM or SQ.

6. "I gave him 2 mg of Narcan®, but then he vomited, became agitated, and had to be restrained."

While we do not suggest leaving a patient in a state of cardiopulmonary depression due to opioid abuse, consider using naloxone in smaller doses (0.1-0.8 mg) if the depressive symptoms are relatively mild and can be assisted by oxygen and slow bagging of the patient and you believe that the patient is a chronic abuser (ask for a history from family, friends, or EMS, and check for track marks on the extremities). The withdrawal effects brought on by large doses of naloxone in the chronic abuser often make the patient agitated and difficult to reason with. Your nursing and security staffs will thank you for your consideration. Vomiting may occur upon arousal, so make sure aspiration precautions are in place.

7. "I thought since he was alert and oriented, he was okay to leave, because he really wanted to. I never thought he'd come back dead!"

A patient walkout in these circumstances could be hazardous to their health ... and to your malpractice insurance! If a patient becomes agitated and wishes to leave the ED against your advice after naloxone treatment, perform a careful assessment of capacity and make sure your risk-management team is involved in the decision-making.

8. "I thought she told me everything she had ingested. I didn't think to send an acetaminophen level."

The ingestion history that you receive from a patient may be incomplete or absent. Assume nothing. Let your physical exam guide, though not rule, your workup. In cases of mixed OD with pills and unknown ingestions, acetaminophen and salicylate levels should be checked, as they are very treatable early in the game.

9. "He was breathing on his own. I didn't think to look at his oxygen saturation."

The persistently hypoxic patient should have a chest x-ray to check for signs of ARDS or pneumonia. An ABG should be obtained to clarify the current PaO2 and PaCO2 status and to help guide disposition. A persistently hypoventilating patient needs more naloxone and is not ready for discharge. If a naloxone drip is required to maintain normal respiratory rate, the patient needs admission or longer observation.

10. "I thought he was just on drugs, so we admitted him for observation. How could I have known he had meningitis?"

The diagnoses of meningitis and encephalitis must be considered in all patients who are lethargic and in whom there is no clear diagnosis, including young people in whom drug use is suspected, but not confirmed. ▲

toxic. In such cases, a trial of a reversal agent is warranted. Naloxone (Narcan®) is a competitive opioid antagonist, blocking all opioid receptors.[165] Naloxone may be given via the intramuscular, subcutaneous, or endotracheal route, if IV access cannot be obtained.[168,169] Different references suggest different dosing regimens, and the initial dose will depend on the circumstances. For practical purposes, a dose of 0.4 mg will reverse most opioid-induced respiratory depression. If opiate dependence is suspected and time permits, a more reasonable starting dose may be 0.1 to 0.2 mg, repeated in these increments and titrated to achieve arousal and respiratory sufficiency without producing withdrawal. In all but a very few cases, if a total of 10 mg of naloxone has been given without resolution of clinical symptoms, then the symptoms are unlikely to be due to opiates (for more information, see Special Circumstances, below). Longer-acting opioid antagonists, such as naltrexone and nalmefene, have a few select uses, such as blocking the effects of opioids in certain patients as part of a drug rehabilitation program, but they have no proven role in the routine management of opioid toxicity in the ED.

Specific Opiates: Long-acting or Designer Agents

Methadone

Methadone is a long-acting opioid, popular in "maintenance" programs (outpatient programs in which patients use methadone to prevent opioid cravings and to prevent physiologic withdrawal). Patients known to be using methadone on a regular basis are, by definition, physiologically addicted to opioids; the indiscriminate use of large doses of naloxone in such patients will produce opioid withdrawal, regardless of the etiology of the patient's symptoms. In such patients, it is reasonable to start with 0.01 mg of naloxone intravenously, and titrate until the patient regains his or her mental status or begins to develop early signs of opiate withdrawal. As methadone is a long-acting drug, a continuous infusion will likely be necessary. (For more information, see Controversies on page 17.)

"China White"

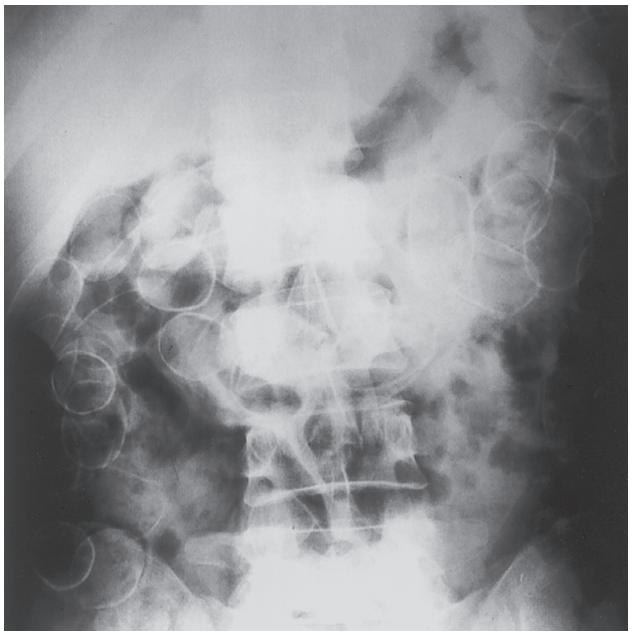
Alpha-methylfentanyl is an extremely potent opioid, the use of which reached epidemic numbers in the 1980s.[170] It is one of the opiates for which large and repeated doses of naloxone may be necessary.[168]

Propoxyphene

Propoxyphene use has declined over the decades due to numerous toxic deaths. The unique properties of propoxyphene include quinidine-like effects on fast sodium channels, and membrane stabilization may produce seizures and cardiac conduction problems in overdose. The cardiac conduction abnormalities usually present as hypotension and QRS prolongation, and should be treated with intravenous sodium bicarbonate (1-2 mEq/kg IV). Large doses of naloxone may be needed to correct respiratory depression. Seizures should be managed initially with benzo-

Figure 1. Body Packing.

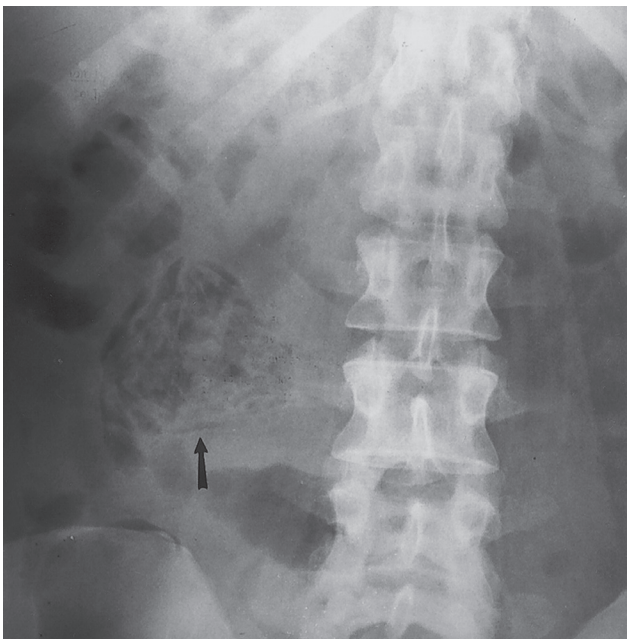
Radiographs of an adult smuggling drugs shows relatively opaque packets in the transverse colon.



*Source: Hunter TB, Taljanovic MS. Foreign Bodies. *Radiographics*. 2003 May-Jun; 23(3):731-757. Figure 24b.

Figure 2. Body Packing With Rubber Gloves.

Radiograph of an adult who was in the habit of swallowing rubber gloves shows a mottled lucent area (arrow) in the right lower quadrant of the abdomen. The finding represents a rolled-up rubber glove in the terminal ileum. It has a similar appearance to swallowed drug packets.



*Source: Hunter TB, Taljanovic MS. Foreign Bodies. *Radiographics*. 2003 May-Jun; 23(3):731-757. Figure 24d.

diazepines, with the addition of barbiturates or propofol in the event of benzodiazepine failure; there is no role for phenytoin or similar agents.

Pentazocine

Pentazocine is a combined opioid agonist and antagonist whose toxicity is characterized by rapid onset and the need for prolonged observation. Large doses of naloxone (10 mg IV) may be required, and clinicians should have a low threshold to admit these patients.[166,168]

Special Circumstances

Body Packers and Body Stuffers

Body packers swallow large quantities of well-wrapped illegal drugs (typically heroin or cocaine), with the intention of smuggling them into a destination country and excreting them after arrival. Occasionally, rectal or vaginal packing is seen. Patients may present with evidence of drug toxicity (from leaking packets), intestinal obstruction, or without symptoms but in the custody of law enforcement agents.

A detailed history should be elicited, if possible, including the type of drug and number of packets. Not surprisingly, however, the patient may choose to disclose very little.[171,172] The physical examination may reveal evidence of a sympathomimetic (cocaine) or opioid (heroin) toxidrome; in addition, the abdominal exam may reveal evidence of packets, signs of obstruction, or peritonitis in the event of packet rupture.

Radiographic evaluation should proceed once the patient is stabilized. (See **Figure 1** and **Figure 2**.) The best initial screening test is a plain abdominal x-ray, which has a reported sensitivity of 75-95%.[172] Specific signs, including the "double condom" sign (air trapped between the layers of the condom) or "rosette" sign (air trapped in the knot of the tied condom) may be present and assist in the diagnosis.[172] Noncontrast CT scanning or barium-enhanced radiography is more sensitive for the detection of packets. They can be useful when a plain radiograph is equivocal, although packets missed by this method have likewise been described.[172]

Treatment of the asymptomatic patient consists of whole bowel irrigation. until all packets are believed to have passed; a repeat abdominal CT should be performed to document evacuation of the gastrointestinal tract.[172] Patients with heroin toxicity from packet rupture can be stabilized with high-dose naloxone; because of the enormous amount of heroin released from the rupture of just 1 or 2 packets, naloxone doses in excess of 10 mg may be needed.[172] Once stabilized, these patients can then be treated with whole bowel irrigation until the packets have passed. Patients with cocaine toxicity from packet rupture should be emergently stabilized and brought to the OR for surgical decontamination of the GI tract. Patients with evidence of bowel obstruction or peritonitis will also require surgical intervention.[171]

Body stuffers differ from body packers in that they hastily swallow poorly wrapped drug when they fear detection or arrest is imminent. Although these patients ingest less drug than body packers, they are more likely to become symptomatic due to the poor packaging. Symptomatic patients should be treated in the same manner as symptomatic patients noted above. Asymptomatic patients should be observed for at least 6 hours, although many practitioners routinely admit these patients for observation over a 24-hour period.

Controversies

Prehospital/Empiric Use of Naloxone

Naloxone is frequently used as part of the EMS "coma cocktail" (which also includes 50% dextrose and thiamine). Two prehospital studies showed that naloxone is the fourth most-used agent by ALS units, after hypoglycemic therapy (D50 and glucagon), nebulized $beta_2$ agonists, and nitroglycerin tablets.[173,174] At least 2 studies have reported that the majority of patients treated with out-of-hospital naloxone had no clinical benefit from treatment.[174,175] One of these studies, however, did document a high safety profile (5 nonfatal complications associated with its use in > 800 prehospital patients).[175] It is possible that difficulties identifying patients who are clinically intoxicated with opioids, as well as the presence of mixed intoxications, contributed to the lack of documented clinical response to prehospital naloxone;[175] oftentimes naloxone is given

Key Points For Treating Patients With Suspected Toxicity From Drugs Of Abuse

- The ABCs of supportive care are critical for these patients. Always remember them first.
- Use all resources possible to obtain history of ingestion/abuse by the patient.
- Consider antidotes and decontamination, where appropriate.
- Consider mixed ingestions and watch out for complications of the acute toxicity and concomitant medical issues (trauma, hypothermia, etc).
- The patient's history as well as mental status and pupil exam can often give answers regarding unclear intoxications and their depth, as well as guide treatment for the patient.
- With good supportive care and observation, most patients with toxicity from drugs of abuse will clear without significant long-term complications. ▲

to patients with altered mental status per EMS protocols without consideration of clinical parameters, such as respiratory rate and pupil size. Despite the mixed data regarding efficacy, naloxone is likely to remain part of the prehospital armamentarium as a diagnostic/therapeutic agent in the evaluation and treatment of altered mental status.

Observation Time in the ED after Naloxone Use or Use of Naloxone Drips in Opioid Intoxication

Naloxone has a duration of action up to 1 hour, when given intravenously. If a patient has a normal mental status and normal respiratory rate after administration of naloxone, he or she can be considered for discharge home, though the observation time quoted for safe discharge from the ED after naloxone administration varies between 1 and 6 hours.[165,166,168,169] When opioid toxicity recurs, however, repeat naloxone and a continuous naloxone infusion should be administered. In one series of 84 patients with presumed opioid toxicity, 50% of whom responded to an initial dose of naloxone, 31% experienced a recurrence in signs of opioid toxicity.[176] Recurrent opioid toxicity likely represents intoxication with a long-acting drug or — a less likely possibility — ongoing absorption from the gastrointestinal tract.

Any patient who receives a second dose of naloxone in the ED should be placed on a continuous infusion and admitted. The appropriate amount is 2/3 of the dose to which the patient initially responded, administered every hour by continuous infusion. The infusion rate should then be reduced, as tolerated. If the patient has normal hemodynamics, respiratory rate, pulse oximetry, and mental status 1 hour after the infusion is stopped, then discharge is acceptable.

Physostigmine as a Reversal Agent in GHB Intoxication

Although most cases of GHB intoxication can be managed conservatively, severe overdoses may present with profound respiratory depression and coma requiring endotracheal intubation. An antidote, if available, would make such interventions unnecessary.

Physostigmine is a reversible inhibitor of acetylcholinesterase and has been described as a reversal agent for GHB, both in the anesthesia setting[177] and in the ED.[178] A recent review of the published literature, however, noted that all the evidence for humans is anecdotal, with no control group; the time course described for awakening from GHB-induced sedation after administration of physostigmine appears similar to that reported for GHB without physostigmine. Further, there is no evidence that GHB-sedated patients given physostigmine have a better outcome than patients treated with supportive measures alone.[179] In addition, recent studies in GHB-intoxicated animal models show no effect of physostigmine on arousal, but do show that it produces cholinergic toxicity.[180] Given that physostigmine may precipitate a cholinergic crisis if administered injudiciously, and that it may cause bradycardia or seizures if given too quickly, the weight of the evidence at this time argues against physostigmine for reversing GHB-induced sedation.

Disposition

Most acutely intoxicated patients need only supportive care to regain normal function. Full recovery is observed in most patients within several hours after exposure. Strict attention to the ABCs, with frequent reassessments and appropriate monitoring, are therefore essential in these cases. A majority of authors agree that a patient with persistent symptoms 6 hours after ingestion deserves consideration for further diagnostic workup and admission. Patients who remain comatose or exhibit continued bizarre behavior, as well as patients with evidence of seizures or cardiovascular dysfunction, should be admitted to an intensive care unit for continued supportive care and monitoring. ▲

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available.

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Physician CME Questions

65. As part of the initial evaluation of the intoxicated patient, all of the following may help identify the drug used, *except*:
a. description of patient surroundings by EMS personnel
b. abnormalities in vital signs
c. pupillary reaction
d. auscultation of heart sounds
e. inspection of skin and mucous membranes

66. The 2 most important bedside tests, which should be obtained immediately in any suspected drug-intoxicated patient, are:
a. urine toxicology screen and myoglobin
b. CT scan of brain and chest x-ray
c. fingerstick and electrocardiogram
d. fingerstick and urine toxicology
e. electrocardiogram and urine myoglobin

67. A 35-year-old woman walks in complaining of sudden onset of chest pain. The family tells you they found her on the floor with a pipe in her hand. Her blood pressure is elevated to 240/120, and an electrocardiogram demonstrates ST segment elevations of the anterior leads. Appropriate treatment for this patient includes all of the following, *except*:
a. nitroglycerin
b. benzodiazpines
c. oxygen
d. metoprolol
e. nitroprusside

68. You have administered the correct medications described above in question 67, and the patient continues complaining of chest pain. Her blood pressure is now 160/100, and the ST segment elevations remain unchanged. All of the following steps are appropriate in the continued management of this patient, *except*:

a. labetalol
b. phentolamine
c. cardiology consultation and cardiac catheterization
d. chest x-ray
e. morphine

69. Management of stimulant-induced hyperthermia includes all of the following, *except*:

a. sedation with antipsychotics and benzodiazepines
b. keeping the patient in a quiet but well-monitored room
c. intravenous fluids
d. aggressive external cooling measures
e. monitoring urinary output

70. Which of the following is true regarding LSD?

a. LSD use was popular in the 1960s, but has steadily decreased since the 1970s
b. The strength of LSD samples today is considerably higher than in the '60s and '70s.
c. Patients with LSD intoxication are typically disoriented
d. The effects of LSD intoxication usually last from 6 to 12 hours.

71. GHB withdrawal:

a. like opioid withdrawal, is uncomfortable, but not life-threatening.
b. is rarely associated with vital sign instability.
c. does not lead to mental status changes.
d. management is similar to benzodiazepine or alcohol withdrawal.
e. only requires small doses of a sedative agent in symptomatic patients.

72. All of the following are true regarding GHB and its prodrugs, *except*:

a. Intoxicated patients typically present to the ED secondary to CNS depression
b. Myoclonic activity is indicative of seizures.
c. Respiratory depression and prolonged apneic episodes may occur.
d. Gastrointestinal symptoms are common in intoxicated patients.

73. Phencyclidine:

a. does not cause seizures.
b. induced hypertension never responds to anxiolytics.
c. typically causes hypothermia when ingested alone.
d. intoxication most commonly causes nystagmus and hypertension.

74. A 20-year-old college student is brought to the ED drowsy and vomiting. His friends tell you he had been dancing and drinking all night. On exam, you find a well-hydrated male who is minimally responsive and has alcohol on his breath and dilated pupils. He occasionally smacks his lips, in between vomiting episodes. Appropriate management would include all, *except*:

a. dextrose test determination
b. brain CT
c. obtaining an electrocardiogram
d. obtaining serum chemistry
e. aggressive IV hydration

75. Ketamine:

a. causes nystagmus in most of its users.
b. use does not cause agitation or combativeness.
c. toxicity can lead to apnea and pulmonary edema.
d. use can be ruled out in patients without nystagmus and hallucinations.

76. Which of the following agents reliably produce miosis?

a. heroin
b. demerol
c. methadone
d. a and c
e. all of the above

77. Reliable history of overdose of which of the following agents warrants admission?

a. methadone
b. pentazocine
c. alpha-methylfentanyl
d. a and b
e. all of the above

78. General criteria for admission with opioid overdose include all of the following, *except*:

a. revival from a respiratory arrest
b. asymptomatic body packers, with all packets cleared by history and CT scan
c. failure to wean from a naloxone drip
d. a and c
e. all of the above

79. **Prehospital naloxone:**
    a. is safe for use in patients with altered mental status.
    b. frequently is not efficacious when used.
    c. both of the above.
    d. neither of the above.

80. **Naloxone drips:**
    a. should be initiated if a second dose of naloxone is used in the ED
    b. should be initiated if use of a long-acting opioid is reliably discerned
    c. should be initiated at 2/3 of the previous effective dose given per hour
    d. a and c
    e. all of the above

Coming in Future Issues:

Minor Head Trauma • Hypertensive Emergencies & Urgencies

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Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case-
- control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

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