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The Practical Journal for Emergency Physicians

Emergency Medicine Reports

Volume 22, Number 13 **June 18, 2001**

Drugs of Abuse and Their Complications: Emergency Department Evaluation and Management: Part II

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The ever-expanding options of prescription and non-prescription drugs of abuse have created challenges for emergency practitioners managing patients who are "under the influence." Although some drugs of abuse (e.g., marijuana) rarely cause pathophysiological derangements that are life-threatening, other drugs, including cocaine, benzodiazepines, and inhalants, can cause life-threatening cardiac and/or respiratory emergencies.

Currently, the most common drugs of abuse encountered in patients seen in the emergency department (ED) include cocaine, benzodiazepines, opiates, barbiturates, and amphetamines. Because the histories provided by these patients may be unreliable, effective management requires familiarity with the full range of psychiatric, neurological, and cardiorespiratory manifestations of these agents, and in the case of some drugs, prompt recognition of life-threatening complications.

Although some recreational drugs produce symptoms that resolve on their own, other agents, especially those that produce respiratory depression (benzodiazepines) or cardiac toxicity (cocaine) require specific interventions.

With these issues in clear focus, the purpose of this second and final installment of this series is to present clinical syndromes associated with common drugs of abuse. Strategies for differential diagnosis, indications for invasive intervention, and approaches to patient disposition are presented in a practical, clinically relevant manner.

— The Editor

Sedative-Hypnotics

Drugs that decrease anxiety and induce sleep have long been used and abused. They remain a very popular drug class among substance abusers, both when used alone and in combination with other illicit drugs. As a class, there were nearly twice the number of reports in 1999 to Poison Control Centers for sedative-hypnotic use than for all other drugs of abuse *combined*.[1] They are the fourth most popularly abused drug in patients older than age 19, and despite the relative safety of benzodiazepine overdose, ranked fifth in cause of deaths.[1] National Household Survey on Drug Abuse (NHSDA) data from 1999 showed an increase of 132% in the number of new users compared to 1990, with a total of 186,000 new users in 1999.[2] However, these drugs are not as commonly abused as they were in the 1970s and 1980s. There has been an estimated 50% decrease in the total number of lifetime users when comparing data from 1985 to 1998.[2]

Many drugs in this class act via a common receptor: the gamma-amino butyric acid (GABA) receptor complex. GABA is

the principal inhibitory amino acid in the central nervous system (CNS). *(See Table 1.)* These compounds bind to the postsynaptic GABA receptor complex and increase the time the associated Cl channel stays open. This hyperpolarizes the postsynaptic neuron and inhibits its ability to depolarize or reach an action potential. Thus, the sedative, anxiolytic, and anticonvulsant effects of barbiturates and benzodiazepines are thought to be due to GABA-mediated inhibition of CNS neuronal activity.[3]

Barbiturates. Barbiturates were discovered in 1903 after the introduction of barbital, and they quickly became the primary sedative-hypnotic used. Over time, their use has largely been replaced by benzodiazepines. Clinical indications for barbiturate use now are reserved for induction of anesthesia; seizure management; treatment of elevated intracranial pressure; and, in combination with other compounds, for treatment of headache and abdominal pain (scopolamine hydrobromide [Donnatal]). One of the main reasons for this change to benzodiazepine use is the high potential for abuse with barbiturates and the lethal nature of barbiturate overdose. In the 1970s, barbiturates were the most commonly used drug for suicide by overdose.[4] Although abuse rates of barbiturates have declined, the American Association of Poison Control Centers (AAPCC) Annual Report still cites around 5000 exposures and 10 barbiturate deaths annually.[5]

Several factors play into the high abuse potential of barbiturates. In small doses, they produce antianxiety effects and help induce sleep. In larger doses, they create euphoria similar to that experienced with morphine or alcohol. Heroin addicts may take barbiturates with their heroin to increase its effects.[5] Alcoholics, narcotic addicts, hallucinogen abusers, and amphetamine users often use barbiturates in combination with their principal drug of choice to enhance their drug's effects or dampen its undesirable side effects. Abusers of barbiturates also develop tolerance to and physical dependence on the drug. As tolerance builds, they need larger and larger doses to produce the desired effect; when physically dependent, they experience significant withdrawal symptoms that make it difficult to break the habit.

Pharmacology. Barbiturates are classed by their duration of action. The short-acting barbiturates are more lipid soluble, and therefore, enter the CNS quickly. The longer-acting ones enter and leave the CNS more slowly. Barbiturates are weak acids and are more rapidly absorbed in an acidic environment. An alkaline environment promotes ionization of barbiturates and, therefore, decreases their absorption. This concept is the basis for alkaline diuresis, in which alkalinization of the urine "traps" ionized forms of a drug and increases its elimination from the body. Effects of ultrashort-acting barbiturates (e.g., methohexital sodium [Brevital]) begin in 10 minutes and last for 3-4 hours. Intermediate-acting barbiturates take 45 minutes to work, but last for 6-8 hours. An example is butalbital, found in Fiortal. Long-acting barbiturates take 60 minutes to act and last for 10-12 hours. Phenobarbital (Luminal) is a well-known example of long-acting barbiturates. Even though the effects of these drugs are relatively brief, their elimination half-lives are much longer. Short-acting ones have half-lives between 14 and 48 hours, while long-acting agents have half-lives of up to 100 hours.

Barbiturates also cause numerous drug interactions, many of which result from the induction of microsomal p450 liver enzymes. Other drugs that also are dependent on this system for elimination can be affected. Examples of drugs whose metabolisms are enhanced by barbiturate use include coumadin, doxycycline, theophylline, quinidine, digoxin, corticosteroids, and oral contraceptives.[5] Drugs used for seizure treatment also are effected. Valproic acid will increase barbiturate levels, while carbamazepine levels are decreased by barbiturate use. The end result on levels of phenytoin is unpredictable as they may rise or fall in any given individual who uses barbiturates. Finally, patients using barbiturates may be at higher risk of acetaminophen overdose or carbon tetrachloride exposure, as chronic induction of

Emergency Medicine Reports™ (ISSN 0746-2506) is published biweekly by American Health Consultants, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (800) 688-2421 or (404) 262-7436.

Vice President/Group Publisher: Brenda Mooney
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GST Registration No.: R128870672

Periodical postage paid at Atlanta, GA. **POSTMASTER:** Send address changes to ***Emergency Medicine Reports***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $28. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Multiple copy prices: One to nine additional copies, $323 each; 10 to 20 additional copies, $287 each.

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1 year *with* 52 ACEP/AMA/52 AAFP Category 1/Prescribed credits (52 AOA Category 2B credits): $494
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Term of approval covers issues published within one year from the beginning distribution date of 1/00. Credit may be claimed for one year from the date of this issue.

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Table 1. Commonly Abused Sedative Hypnotics

BARBITURATES
Short-acting: e.g., Brevital
Medium-acting: e.g., Seconal, butalbital, Fiortal
Long-acting: e.g., Luminal
BENZODIAZEPINES
Ultrashort-acting: e.g., Versed, Halcion
Short-acting: e.g., Xanax, Ativan
Long-acting: e.g., Librium, Klonopin, Valium, flunitrazepam (Rohypnol)
Longest-acting: Tranxene
OTHER
Sleep aids: chloral hydrate, zolpidem tartrate (Ambien), ethchlorvynol (Placidyl), glutethimide (Doriden), meprobamate (Miltown, Equanil), carisoprodol (Soma)
Methaqualone (Quaalude)

p450 enzymes will enhance production of toxic metabolites from these compounds.

Treatment. Presentation of the patient abusing barbiturates varies with the dose taken and the degree of tolerance present in the user. Lower doses act similarly to alcohol, with users experiencing mild euphoria, drowsiness, and impaired memory and judgment. They exhibit confusion, slurred speech, ataxia, nystagmus, and incoordination. Higher doses (i.e., intentional or accidental overdose) may have profound effects on many organ systems. CNS depression may lead to fatal respiratory depression. Hypotension occurs as a result of inhibition of brainstem centers controlling cardiac output and peripheral vasoconstriction. In large doses, barbiturates also may directly depress the myocardium. Non-cardiogenic pulmonary edema and hypothermia also are present in these patients. Additionally, gastrointestinal motility is decreased and may delay absorption. As the effects wear off and motility returns, the patient may appear to "relapse" as additional drug is absorbed from the gastrointestinal (GI) tract. Cutaneous bullae occur in 4-6% of patients with barbiturate coma and in 50% of patients who die from overdose.[5] The lesions are clear vesicles on an erythematous base often located over pressure sites, and may be a clue to the cause of coma in unresponsive patients. A grading system (grades I-IV) was developed by Reed to classify coma caused by barbiturate overdose.[6] The system grades patients based on their deep tendon reflexes, level of consciousness, and hemodynamic stability. This system also can predict patient prognosis, with most deaths associated with barbiturate overdose seen in grade III or IV coma.

With the multiple organ systems involved, management of patients with barbiturate overdose can be challenging. Mechanical ventilation and hemodynamic maintenance are the primary aspects on which to focus. Patients with insufficient ventilation should be intubated, and hypotensive patients should be given pressors (i.e., dopamine or norepinephrine) if they are still hypotensive after a 1-2 liter fluid challenge. Swan-Ganz catheter placement may be required to further manage hypotension. Hypothermic patients should be actively warmed. Repeated dosing with activated charcoal (2 gm/kg initial dose and 1 gm/kg every 2-4 hours after) and gastric lavage should be performed. Lavage may be useful several hours after overdose as delays in gastric emptying can promote bezoar formation. Urinary alkalinization is recommended for increasing clearance of long-acting barbiturates, but *not* for short- or intermediate-acting ones. Only long-acting barbiturates are cleared by the kidneys. Before instituting alkalinization, the patient should be hydrated adequately to ensure hypotension is not present. A 1-2 mEq/kg IV bolus of sodium bicarbonate is given, and followed by infusion of D5W with 150 mEq sodium bicarbonate added. The infusion is given at a rate to ensure urine output of 1-2 mL/kg/hr (250 mL/hr in the average-size adult). The goal is a urine pH of 7-8, and arterial pH should not exceed 7.55. Hypokalemia may occur as a consequence of this treatment and should be corrected if present. One recent study found that repeated dosing with activated charcoal was more effective than urinary alkalinization in a simulated overdose setting.[7] Another recent article supported that hemodialysis is more effective than hemoperfusion for patients with severe barbiturate toxicity.[8] It was previously believed that hemoperfusion was a better approach for highly protein-bound drugs (i.e., phenobarbital).

It is important to remember that, in general, quantitative barbiturate serum levels do not correlate with the patient's symptoms or prognosis. This occurs because most barbiturates have a large volume of distribution, and therefore, serum levels do not accurately reflect CNS levels. Chronic exposure to barbiturates also can cause variation with symptoms and serum levels. Therapeutic phenobarbital levels are up to 40 mcg/mL; a level of 50 mcg/mL may produce only light sedation in a chronic user, but deep coma in a first-time exposure. A few exceptions are noteworthy. Short-acting barbiturate levels of greater than 35 mcg/mL are considered potentially fatal, as are intermediate-acting levels of greater than 50 mcg/mL. Phenobarbital levels of greater than 80 mcg/mL also are potentially fatal. These levels may be helpful for assessing patient risk with significant barbiturate overdose.

The barbiturate withdrawal syndrome is similar to alcohol withdrawal. Minor abstinence symptoms of restlessness, anxiety, insomnia, depression, vomiting, sweating, and tremor can occur within 24 hours of last use and can persist for 3-7 days. Major abstinence symptoms can appear 2-3 days after last use, and include generalized tonic-clonic seizure, auditory hallucinations, delirium, hyperpyrexia, cardiovascular instability, and death. Symptoms are best treated by phenobarbital loading followed by a gradual taper with inpatient monitoring.

Benzodiazepines. Benzodiazepines have become widely popular (and widely abused) as sedative-hypnotics since their first use in the 1960s. They are used to treat acute seizures, agitation, anxiety, and alcohol withdrawal, and as sleep-aids. As they cause much less respiratory depression in overdose, they are safer than barbiturates. In additional comparison to barbiturates, they do not significantly stimulate the hepatic p450

enzyme system and, therefore, do not affect drug levels of other compounds. They are, however, metabolized in part by p450 oxidation and some drugs (i.e., cimetidine) do affect elimination of certain benzodiazepines.[9] Patients with serious liver impairment from cirrhosis or hepatitis also will have altered pharmacokinetics.

Benzodiazepines are thought to work by post-synaptic enhancement of GABA inhibition in the CNS, but a large number of peripheral binding sites for benzodiazepines also have been discovered.[10] These sites have been identified in liver, lung, renal, and cardiac tissue. The peripheral binding sites lie on the mitochondrial surface membrane instead of the cell surface membrane. Their exact role is unclear but could be responsible for some of the cardiovascular effects of benzodiazepines.

Like barbiturates, benzodiazepines also are classed by their half-lives. Ultrashort-acting midazolam hydrochloride (Versed) and triazolam (Halcion) have the shortest duration of action and their effects last only about an hour. Short-acting alprazolam (Xanax) and lorazepam (Ativan) are next, with effects lasting several hours. Long-acting chlorodiazepoxide hydrochloride (Librium), clonazepam (Klonopin), and diazepam (Valium) have effects lasting many hours. The benzodiazepine with the longest effects is chlorazepam (Tranxene) whose half-life is 30-200 hours and does not reach peak serum levels for 46-78 hours.[11] Many benzodiazepines produce one or more active metabolites and significantly prolong their effects compared to the half-life of the parent compound.

Benzodiazepines are a very frequently abused class of drugs. The AAPCC Annual Report found more than 40,000 exposures with benzodiazepines were reported to Poison Control Centers in the United States in 1999.[1] This number is higher than that found for any other illicit use of a single drug. More than one-half of the reports were associated with intentional abuse, and the majority (29,000) were treated in a health care facility.[1] These drugs commonly are mixed with alcohol to enhance each other's effects. Like barbiturates, they also are taken with heroin to enhance the effects of low-quality heroin. A more sinister aspect of benzodiazepine abuse has taken form in the past decade: to aid in sexual assault. Short-term memory loss is associated with some benzodiazepines, and Flunitrazepam (Rohypnol) has gained wide-spread notoriety as a "date-rape drug."[12]

Even with the high numbers of patients abusing benzodiazepines, they remain relatively safe drugs. Only 65 deaths were reported by the AAPCC in 1999 from the more than 40,000 exposures to benzodiazepines.[1] Pure benzodiazepine overdose is known for its relative safety, but the danger increases with co-ingestions. Unfortunately, abuse of other drugs in combination with benzodiazepines is common, and the history in these cases frequently is unreliable. Patients under the influence of benzodiazepines exhibit somnolence, nystagmus, ataxia, hyporeflexia, and mild respiratory depression. Qualitative laboratory testing for the presence of benzodiazepines can be useful to establish their presence, but quantitative tests are unreliable because serum levels do not correlate well with clinical findings. The degree of symptoms present depends more on the presence of co-ingestions of other CNS depressants than the amount of benzodiazepines taken.[13] Management of these patients centers on supportive treatment, including airway support when indicated, fluids followed by pressors for hypotension, and activated charcoal (1 mg/kg). Repeated dosing with activated charcoal has been suggested to be of benefit with longer-acting benzodiazepines, or in patients with reduced liver function.[14]

With the exception of naloxone treatment in opiate overdose, only benzodiazepines have a specific drug antagonist for clinical use. Flumazenil (Romazicon) binds to the benzodiazepine receptor and reverses the clinical effects associated with overdose. Indications for use of flumazenil include reversal of benzodiazepine effects from overdose or therapeutic use in the ED. However, in reality, contraindications and side effects preclude its use in a general fashion. Use of flumazenil can precipitate acute withdrawal and seizures in chronic benzodiazepine users.[15] It is contraindicated in patients with a "mixed" overdose in which the other drugs involved may increase seizure activity (i.e., cocaine, propoxyphene, etc.), in patients with suspected or known head injury, in patients with a known seizure disorder, or in tricyclic overdose.[15] As a comatose ED patient with history of overdose may not be able to provide this information, many ED physicians opt not to routinely give flumazenil as part of a "coma cocktail." When used, it is important to titrate the dose with gradually increasing amounts to produce an effect (0.2 mg IV q 1-2 minutes up to 3 mg total). Also, once a patient is "reversed," physicians should remember that the half-life of flumazenil is around 60 minutes and may be much shorter than many benzodiazepines. If necessary, a continuous infusion at 0.1-0.2 mg/hr may be used.

Like barbiturates, patients taking benzodiazepines for extended times will become physiologically dependent. As the half-life of some benzodiazepines can be quite long, symptoms of withdrawal may not occur for up to one week after the last use. Withdrawal symptoms include anxiety, irritability, insomnia, vomiting, tremor, sweating, and tinnitus. Severe symptoms can occur, including seizures, hallucinations, and delirium. Treatment of withdrawal symptoms is best accomplished by reinstitution of a benzodiazepine followed by slow tapering. To truly accomplish this, many patients will need inpatient addiction treatment.

Other Sedative-Hypnotics. Several non-barbiturate and non-benzodiazepine prescription sedatives exist on the market and deserve mention. Many of these compounds more commonly were used in the 1960s when they were touted as non-addicting sleep aids. Unfortunately, the opposite was found to be true, with many of these compounds being addictive, highly abused, and toxic in overdose. With the exception of chloral hydrate and newer agents, e.g., zolpidem tartrate (Ambien), these drugs largely have been removed from general use. However, they still are found in the United States and are abused by patients.

Chloral hydrate primarily is used as a short-acting sedative in pediatric cases to enable the performance of procedures. It

was much more popular in the 1950s before the introduction of barbiturates. It gained notoriety due to its synergistic effects with ethanol, and was referred to as "knockout drops" or a "Mickey Finn." Patients with chloral hydrate overdose present with CNS and respiratory depression, and cardiovascular instability. Most deaths associated with chloral hydrate result from refractory hypotension or dysrhythmias. Case reports exist of using beta-blockers (propranolol) to treat ventricular dysrhythmias in these patients, as these rhythms often are resistant to standard treatment.[16]

Ethchlorvynol (Placidyl) has a short onset of action (15 minutes) and effects wear off in fewer than five hours. It primarily was prescribed as a sleep aid. It comes as a gelatin capsule, and its liquid contents easily can be extracted for IV use. In overdose cases, patients experience respiratory depression, mild hypotension, and prolonged coma (average duration of 4-5 days). A significant clue in overdose cases is the presence of a strong, pungent, vinyl, or sweet odor on the patient's breath. IV use consistently induces non-cardiogenic pulmonary edema within minutes of injection. Most of the fatalities result from complications of prolonged coma. When treating a patient with ethchlorvynol overdose, it is important to remember that hemodialysis is ineffective for drug removal, and blood levels of the drug do not correlate well with toxicity.

Glutethimide (Doriden), another drug popular in the 1950s and 1960s, is seldom prescribed today and virtually is only a drug of abuse. Symptoms begin within 30 minutes and may persist for up to 40 hours in the overdose setting. Like other drugs in this section, abuse causes respiratory depression, prolonged coma (100 hours), and hypotension. However, it also causes an anticholinergic syndrome, which may provide a clue to its presence. Refractory hypotension often is the cause of early death, with complications of prolonged coma causing later deaths. A distinction with glutethimide overdose is that the coma is often cyclic in nature. This is thought to be due to a cycle of drug absorption, decreased GI motility, and metabolism of the drug, which is followed by return of GI absorption to restart the sequence. Another important fact is that the normal dose of glutethimide is 0.5-1.0 grams, and that overdoses of only 5 grams have been fatal.[2]

Meprobamate (Miltown, Equanil) was popular in the 1950s as a muscle relaxant, and is not widely prescribed now. However, it is structurally similar to carisoprodol (Soma), which is widely prescribed and abused. Both drugs have a rapid onset of action, and a duration of 4-6 hours. Both drugs cause CNS and respiratory depression, hypotension, and cardiac dysrhythmias. Meprobamate is well-known to form GI bezoars, and patients with these may experience cyclic coma as with glutethimide. Multi-dose activated charcoal and hemodialysis both have been used successfully for treatment of severe overdose.

Methaqualone (Quaalude) is a drug that was very popular for abuse in the 1960s and 1970s. The drug was abused for its superior "high" (compared to heroin), to blunt effects of a cocaine "crash," and as an aphrodisiac. Methaqualone was so popular for abuse that its manufacture was halted in the United States in 1984. It still is produced in Europe and smuggled to the United States. Symptoms begin within 30 minutes of use and last up to eight hours, but can be markedly prolonged in an overdose setting. Mild intoxication is similar to alcohol, with slurred speech, nystagmus, and incoordination causing frequent encounters with nearby walls (hence the street name "wallbanger"). Unique features of methaqualone overdose include lack of significant respiratory depression or cardiovascular symptoms. Also, muscle tone and reflexes are paradoxically increased, and may progress to generalized tonic-clonic seizures. Seizures can be treated with benzodiazepines, but may require phenytoin. Barbiturates should not be used, as they can worsen effects of the overdose. Severe overdose also may induce non-cardiogenic pulmonary edema, but most deaths from methaqualone use result from trauma that is associated with the abuser's lack of judgment while under the influence.[5]

Newer agents, e.g., zolpidem tartrate (Ambien), recently have been introduced and have significant differences from other sedative-hypnotic drugs. Zolpidem is used to treat insomnia, and although it is structurally not related to benzodiazepines, its effects are mediated through the benzodiazepine w-1 receptors in the CNS. Overdose causes CNS and respiratory depression, and symptoms are additive when combined with alcohol or other sedatives. Treatment of zolpidem overdose also is supportive, although flumazenil has been used to reverse the CNS and respiratory depression.[18] Although no fatalities have been attributed to buspirone, a case report of two deaths linked to zolpidem overdose has been published recently.[19]

Inhalants

Inhalation of solvent vapors is a very common form of substance abuse, and is especially popular with adolescents. Further, the number of people abusing inhalants has risen dramatically in the past 10 years. In 1990 there were approximately 390,000 new inhalant abusers, and this number rose to 991,000 in 1998. This is an increase of 154%, and the second-highest rise in use compared to all the other drugs of abuse.[1] According to the NHSDA, in 1998 there were 12.6 million lifetime users, or 6% of the 218 million represented by the survey.[1] Of these users, 2 million had used within the last year, and 713,000 within the last month.[1] Inhalants are the only class of illicit drugs used more commonly by teenagers than adults, and the numbers are more alarming when broken down by age category. The Partnership for Drug Free America surveyed teenagers (grades 7-12) and found in 2000 that 21% reported lifetime use, 13% reported use in the past year, and 7% reported used in the past month. The Monitoring the Future Study of 8th- through 12th-graders found that in 1997 lifetime inhalation abuse was higher in 8th-graders (21%) than in 12th-graders (16%).[20] Further concern is caused by reports that link early inhalant abuse with increased use of other illicit drugs (cocaine, opiates, and sedative-hypnotics) in the future.[21]

One of the reasons inhalant abuse is so popular is that the substances abused are readily available, legally obtained, and cheap. More than 1000 common household products can be

Table 2. Commonly Abused Inhalants

COMMON SOURCES	TOXIC COMPOUNDS
A. SOLVENTS:	
Paint thinners	Toluene
Cleaning fluids	Carbon tetrachloride, naphtha, toluene
Gasoline	Gasoline, lead
Glues	Acetone, toluene, *n*-hexane, xylene
Typewriter correction fluid	Tetrachloroethylene, trichloroethane
Felt-tip markers	Naptha, toluene, xylene
B. GASES:	
Butane lighters	Butane
Propane tanks	Propane
Refrigerant gases	Freon
Aerosol propellants	Fluorocarbons, trichloroethylene, nitrous oxide, and toluene
Medical anesthetics	Nitrous oxide, chloroform, halothane, ether
C. NITRATES:	
Cyclohexyl nitrate	
Butyl nitrate	
Amyl nitrate	

abused as inhalants. Substances used for inhalation abuse are hydrocarbon-based and gaseous or volatile at room temperature. Some of the most frequently abused compounds can be divided into solvents, gases, and nitrites. Table 2 summarizes commonly abused inhalants and their toxic ingredients. Aerosol propellants commonly include spray paint and hair spray. Amyl nitrate is sold by prescription only, but butyl nitrate causes similar effects and currently is sold without prescription as a "liquid incense" or a "room oderizer." Different age groups have different substances they prefer to inhale. Teenagers most commonly abuse gasoline and glues, while adults prefer nitrous oxide and amyl nitrate. One study of 285 incarcerated youths found the five most commonly abused inhalants were: gasoline (57%), freon (40%), butane lighter fluid (38%), glue (29%), and nitrous oxide (23%).[22]

Inhalants can be abused by "sniffing" or "huffing." Sniffing involves breathing the fumes directly from an open container, while huffing is done by placing the open container or a rag soaked with the substance into a bag where the vapors concentrate before being inhaled. Both techniques are effective, and a study of 285 incarcerated youths found 60% preferred huffing to sniffing.[22] Users repeat inhalations until the desired effect is achieved. Acute intoxication develops quickly as the extensive pulmonary vasculature allows blood and CNS levels to peak rapidly, similar to IV drug use. The effects are similar to alcohol or other CNS depressants, with the user feeling euphoria, loss of inhibition, relaxation, and sometimes, hallucinations. Clinically, the users have slurred speech, loss of motor coordination, nausea, vomiting, headache, wheezing, and unconsciousness.

Treatment of inhalant complications starts with recognition that the patient has been abusing inhalants. The physician can identify a user by paint stains on the mouth or clothes, a runny nose with sores around the mouth, and by chemical odor on the breath. Asymptomatic patients suspected of inhalant abuse should be monitored for six hours and have screening labs performed, including chest x-ray, arterial blood gas, and liver function tests, and electrolytes should be considered to identify occult damage from chronic abuse. Patients with evidence of respiratory, cardiac, or metabolic imbalances from inhalant abuse should be admitted for treatment and observation.

Toxic effects from inhalation abuse depend, in part, on the substance abused. Some side effects of inhalant abuse are reversible: asthma exacerbation and liver and kidney damage from toluene and chlorinated hydrocarbons (trichloroethylene from typewriter correction fluid, and/or cleaning fluids). Other damage is permanent.[23] Breathing high concentrations of vapors can lead to simple asphyxia. Hydrocarbons are well-known to produce a chemical pneumonitis,[24] which can further exacerbate hypoxia. Hearing loss is associated with toluene and trichloroethylene abuse. Renal tubular acidosis, with hypokalemia and hyperchloremic metabolic acidosis, has been seen in chronic toluene abusers as well.[25] Toluene abuse also causes CNS damage, and peripheral neuropathies are common after repeated hexane (glues, gasoline) and nitrous oxide abuse. Benzene exposure from gasoline can damage bone marrow. A case report exists of several young men receiving airway burns and smoke inhalation injuries from abusing gasoline.[26] In addition, laryngeal edema and spasm have been associated with butane abuse.[27]

The most serious effect is sudden cardiac death, which is most common with glues, typewriter correction fluid, fluorocarbon, and butane gas abuse.[28] "Sudden sniffing death" was first recognized as a complication of inhalant abuse in 1970, with a report of 110 deaths thought to be caused by asphyxia.[29] These lethal events are very unpredictable and are just as likely to happen after first use as after 100th use. The proposed mechanism is death by ventricular arrhythmia, presumably from myocardial catecholamine sensitization or hypoxia-induced heart block. Often, the abuser participates in a strenuous activity (i.e., running from authorities) immediately after abusing solvents. The hyperadrenergic state produced, combined with the sensitization of myocardium, leads to lethal arrhythmias. It is very important for the emergency physician to note that ventricular arrhythmias caused by inhalant abuse are reported to be resistant to advanced cardiac life support (ACLS) therapy. Given the proposed mechanism of catecholamine sensitization and excess, epinephrine is contraindicated in these patients. At least one author suggests using beta-blockers instead of epinephrine to resuscitate them.[30]

Several specific inhalants deserve special mention. Gasoline very commonly is abused as an inhalant, and is most popular in young boys (ages 10-15 years) from economically devastated,

Table 3. Commonly Abused Hallucinogens

PSYCHEDELICS
Lysergic acid diethylamide (LSD)
Mescaline (peyote buttons)
Psilocybin (hallucinogenic mushrooms, *Psilocybe* sp.)
MARIJUANA
Derived from leaves/flowers of *Cannabis sativa* plant
PHENCYCLIDINE (PCP)
Pill form; smoke on marijuana, oregano, or tobacco
ENACTOGENS OR HALLUCINOGENIC AMPHETAMINES
Benzedrine
Designer drugs: MDMA, GHB ("Grievous Bodily Harm," "Liquid X," "Liquid Ecstasy," "Growth Hormone X," etc.), GBL (converted into GHB by body; found in floor cleaning products, nail polish, extra-strength adhesive [e.g., Super Glue] removers)
Methamphetamine ("Ice," "Crystal," "Glass"), methcathinone, STP, MDEA
Methylphenidate (Ritalin)

rural areas.[31] It is a mixture of hydrocarbons with various additives (lead, rust inhibitors, alcohol). Inhalation of only 10-20 breaths can produce effects for up to five hours. Other than CNS depression, vomiting, and ataxia, chronically abusing leaded gasoline can produce lead poisoning, encephalopathy, dementia, and organic psychosis.[32] Sudden sniffing death has been reported as well, but is not as common as with other substances. Burn injuries also are common from gasoline abuse, as users often spill the gasoline around flames, and are slow to respond when their clothes ignite.[33] Among various chlorinated hydrocarbons, trichloroethane is one of the most commonly abused solvents. Trichloroethane is found in cleaners, degreasers, dry-cleaning agents, and typewriter correction fluid. Correction fluid contains 52% trichloroethane, and fatalities have been reported from CNS and respiratory depression. Finally, methylene chloride is found in paint strippers and in Christmas tree bulbs. It appears to be the only hydrocarbon that is not associated with myocardial sensitivity, but is metabolized to carbon monoxide. Serum levels of carbon monoxide peak around 3-8 hours after abuse,[34] and standard treatment with 100% oxygen and hyperbaric oxygen is recommended.

Hallucinogens

Hallucinations are defined as a "sensory experience that does not exist outside of the mind."[35] Hallucinogens have long been used in religious practices to attain altered states of consciousness. Mescaline-containing tops of the peyote cactus, called peyote buttons, are a prime example. Peyote has been used in Native American religious ceremonies for 8000 years,[36] and use by members of the Native American Church is legal in some states. The effects of peyote are similar to lysergic acid diethylamide (LSD) and while sometimes taken by illicit drug users, the nausea, vomiting, and marked bitter taste associated with peyote discourage casual users.

Hallucinogens were most popular with the LSD epidemic of the 1960s. The heightened drug use in the 1960s led to establishment of the National Institute on Drug Abuse, and general campaigns of prevention, strict laws, and enforcement to reduce illicit drug use. There are an estimated 21 million people in the United States who have used hallucinogens in their lifetime. In 1999, an estimated 900,000 Americans were current (used in the last month before the survey) hallucinogen users.[2] This represents 0.4% of the population age 12 and older. Although overall number of users had dropped since the 1960s, hallucinogen use in the 1990s has steadily increased. The number of new users increased 92% from 1990 to 1998. There were an estimated 1.2 million new hallucinogen users in 1998, nearly twice the average annual number during the 1980s. The highest rates of use are reported in 18- to 25-year olds (7% reporting use in the past year), followed by 12- to 17-year olds (4%), 26- to 34-year olds (1%), and those older than age 35 (0.2%).

Hallucinogens represent a very diverse class of illicit drugs. While many different kinds of drugs are capable of producing hallucinations, there are four primary classes of hallucinogenic drugs: psychedelics, marijuana, phencyclidine (PCP), and enactogens or hallucinogenic amphetamines (3,4-methylenedioxymethamphetamine [MDMA]).[36] *(See Table 3.)* The term enactogen was coined by psychoanalysists to refer to the "enhancement of communication" that MDMA produces. The hallucinogenic amphetamines will be discussed in the amphetamine section under "club drugs." LSD is the most commonly abused hallucinogen, with an estimated 17 million lifetime users, and is followed by psilocybin (12 million), PCP (7 million), and mescaline (6 million).

Lysergic Acid Diethylamide (LSD). LSD is the prime example of a psychedelic drug. First synthesized by a Swiss chemist, Albert Hoffman, in 1938, its hallucinogenic properties were not discovered until 1943 when he accidentally spilled some on his hands and took the first "acid trip" bicycling home.[37] LSD is the most potent hallucinogen known with doses in the range of 30 to 50 micrograms producing hallucinogenic effects. Even with such potency, there have been no reported deaths from LSD overdose directly, only injuries and death from dangerous behavior induced by poor judgment. LSD is well absorbed from the GI tract and mucous membranes. The most common route of administration is ingesting LSD dried on small pieces of blotter paper ("blotter acid"). Multitudes of designs are placed on the blotter paper, and the actual amount of LSD on a given piece is unknown. LSD also is sold on small tablets ("microdots"); liquid forms placed on sugar cubes are not widely available today. The Drug Enforcement Agency (DEA) reports that most of the LSD consumed in the United States is produced by fewer than a dozen clandestine labs located in Northern California.

The mechanism of action of LSD is similar to other psychedelics like mescaline (peyote buttons) and psilocybin (hallucinogenic mushrooms). All of these drugs appear to act on postsynaptic membranes of CNS serotinergic neurons. Among other actions, LSD binds to the postsynaptic membrane to increase

serotonin binding time at receptors. Although it is LSD's interaction with the serotinergic system that has long been thought to be responsible for its hallucinogenic properties, more recent research is questioning the role of LSD's action on dopaminergic neurons.[38] This research suggests hallucinations are produced by a complex effect on both neurotransmitter systems. Once ingested, symptoms appear in 30 minutes and last up to 12 hours, with the most dramatic hallucinations appearing in the first four hours post-ingestion.

Clinical effects of LSD vary significantly with the user's surroundings, expectations, and past experiences. When taken in a peaceful, relaxed environment, users report distortions and intensification of colors and sounds. They experience euphoria and generally "altered perceptions of reality" (i.e., normal objects appear novel and exciting, colors can be heard and sounds smelled, and it becomes difficult to distinguish between objects and self). When visual hallucinations are experienced, users are typically aware they are hallucinating. When users take the same drug under stressful circumstances, they often have unpleasant experiences ranging from dysphoria to panic attacks. As the expected reactions of LSD rarely prompt users to seek help, the unexpected and unpleasant reactions can bring users to the ED. Physical findings in these patients are a result of a mild increase in sympathetic tone. Users have dilated but reactive pupils and mildly increased heart rate and blood pressure. True psychotic episodes triggered by LSD use are rare, and should be treated in similar fashion to a non-LSD related event. Flashbacks, or a brief return to the LSD experience, can occur months to years after use. These events are now termed "posthallucination perception disorders" and rarely prompt ED treatment. Treatment of patients under the influence of LSD consists of placing the patient in a quiet, non-threatening area with non-intoxicated friends if possible. Mild sedation with short-acting benzodiazepines may be helpful, and the focus is to protect the patient from potentially dangerous behavior until the effects of LSD wear off. Nearly all patients may be safely discharged with relatives or friends at this point.

Marijuana. Derived from the leaves and flowers of the *Cannabis sativa* plant, marijuana is the most commonly used illicit drug in America. When dried, the leaves and flowers become a tobacco-like substance that is smoked in hand-rolled cigarettes (joints) or put into hollowed-out cigars (blunts). Marijuana can be processed into hashish, or a purified, condensed form, which also is smoked or cooked in food. Marijuana has been used for 12,000 years and was probably one of the first plants cultivated by humans.[36] Marijuana also can be consumed orally by cooking into food, most commonly brownies. Even though marijuana is a Schedule I drug (i.e., no accepted medical uses), there are many who argue that evidence exists for medical uses of marijuana. When tetrahydrocannabinol (THC), the active ingredient in marijuana, is extracted and taken in pill form (dronabinal [Marinol]), it is reported to help lower intraocular pressure in glaucoma and reduce the nausea and/or vomiting seen with chemotherapy treatment.[39] The debate concerning medical uses of marijuana and decriminalization continues to be a source of controversy. Marijuana is imported from Mexico, South America, and the Far East. However, Kentucky, California, Florida, Oregon, and Alaska are five states where indoor cultivation is a significant problem. Some estimates put marijuana in the top five, if not as the No. 1, cash crop in several of these states.

In 1990, there were an estimated 56 million Americans who had tried marijuana, and nearly 20 million used it in the past year.[1,39,42] The most recent estimates from 1998 show 73 million Americans have tried marijuana, or 33% of the population age 12 and older. During the 1990s the number of current users fell slightly, with the 1999 NHSDA data reporting the number of yearly users was 19 million. Marijuana's popularity with illicit drug users is underscored by the 1999 NHSDA estimate that 75% of current illicit drug users (11 million) used marijuana in the last month.[2] The majority of these people (57%) used marijuana alone. Only alcohol (105 million or 47% of population age 12 and older) and tobacco (66 million or 30% of population age 12 and older) were used more frequently than marijuana. The number of new users has increased 63% from 1990 to 1998, and this increase primarily is fueled by the young. The rate of new users in the 12- to 17-year age group doubled from 1991 to 1998, and is even higher than the peak rates of the 1970s. The 1999 Monitoring the Future study found that an alarming 49% of high school seniors reported using marijuana at least once.[20] This compares to 41% of 10th-graders, and 22% of 8th-graders.

THC is the active ingredient in marijuana, and according to the DEA, the THC content of marijuana in the United States has risen from an average of 3.2% in 1977 to 12.8% in 1997. At least two receptors for cannabinoids have been identified.[40] The type I receptor is found in the CNS, while the type II receptor is found in the periphery. These authors find a complex interaction with the two receptors and the cytokine system.[40] Some authors feel the toxicity of THC has been underestimated and report that THC induces neuronal damage and death in the hippocampus, a region of the brain tied to memory.[41] They also feel marijuana shares a common final pathway with morphine, ethanol, and other drugs of abuse as it also has been shown to enhance dopaminergic drive in the CNS.[41] The exact mechanism of action by which cannabinoids produce the effects seen in marijuana users remains to be elucidated.

The clinical effects of marijuana include mild tachycardia, conjunctival injection, dry mouth, increased hunger, and postural hypotension. Users report mild euphoria; they feel calm, time slows, and sensitivity to the surrounding environment is enhanced. Not surprisingly, users' reaction times are slowed, and judgment, coordination, and attention are impaired. Interestingly, while classed a hallucinogen, marijuana alone does not induce hallucinations. Marijuana contains 10 times the respiratory irritants and more carcinogens than tobacco.[35] Chronic users experience the same health problems as tobacco smokers, including emphysema, chronic bronchitis, and asthma. They may develop these problems at younger ages as well, as mari-

juana contains 3-5 times as much tar and carbon monoxide as tobacco, regardless of its THC content. Panic attacks can occur, but are much less frequent than with LSD, and usually require no treatment or short-term benzodiazepines.

Psilocybin. Hallucinogenic mushrooms are common in the southeastern and northwestern United States; they grow in cow manure. Psilocybin is heat stable, and these mushrooms may be cooked without altering their hallucinogenic properties. Effects are similar to those seen with LSD, but are less intense; users typically ingest from one to five mushrooms at a time. Dysphoric reactions or panic attacks are rare, and they produce no vomiting, as does peyote. The prime danger comes from misidentification of *Psilocybe* species with deadly mushrooms (*Amanita* species). *(For more information on hallucinogenic mushrooms, please see* Emergency Medicine Reports, *Oct. 9, 2000 [Vol. 21, No. 21].)*

PCP. Due to the violent and unpredictable reactions in its users and the variety of medical complications, phencyclidine is considered by some to be one of the most dangerous illicit drugs. PCP was developed in the 1950s as an anesthetic, and was quickly discontinued for human use in 1965 after it was found that 50% of patients reported intraoperative hallucinations and agitation.[37] Emergence from PCP anesthesia also was associated with psychotic reactions that could persist for days in some patients. PCP was used for veterinary use under the trade name Sernylan, until 1978. All PCP used today is produced by clandestine laboratories. The 1998 NHSDA data showed that there were an estimated 7.6 million people who used PCP once in their lifetime, and 346,000 who used it in the past year. PCP is used more often by drug users older than age 18, with the 26- to 34-year age group reporting the highest usage.[42] The Monitoring the Future Study also shows a decrease in 12th-graders using PCP from 13% in 1979 to 4% in 1997.[20]

PCP found its way onto the street as a pill in the 1960s, and quickly gained a reputation as an unpleasant drug. In the 1970s PCP use reached its peak, as users began to sprinkle it on marijuana or oregano and smoke it. Using this approach, they could titrate the dose more effectively and reduce the number of adverse reactions. PCP is a white powder with a distinctive bitter chemical taste, and it easily dissolves in water or alcohol in which users also can soak tobacco cigarettes. PCP is chemically related to ketamine, and the mechanism of action of PCP is thought to be by inhibition of dopamine, norepinephrine, and serotonin reuptake in the CNS. The end result is that PCP disrupts basic functions of the brain that prevent sensory input from being integrated into useful behavior. Onset of symptoms after smoking is around 2-5 minutes, with duration of action around 4-6 hours, but some users may not return to "normal" for up to 48 hours. The fact that PCP is both lipophilic, with a large volume of distribution (6.2 L/kg), and highly protein bound (60%) may account for its longer duration of action in some users.[37]

The clinical presentation of a PCP user varies from catatonia to extreme violence, which may make it difficult for the ED physician to recognize. A review of 1000 cases from 1981 found that two physical findings were seen in almost 60% of patients: nystagmus and hypertension.[43] Nystagmus most commonly is vertical in nature, but can be horizontal or rotary. An unusual feature with PCP is that nystagmus is seen in relatively awake patients, while nystagmus from other CNS depressants only will be seen in patients who already are heavily sedated.

The clinical effects of PCP fall into two categories: behavioral and medical complications. The behavior effects of PCP include coma, catatonia, psychosis, and acute confusion. Coma from PCP use often follows violent and bizarre behavior, and the patient may return to these behaviors when emerging from the coma. In one study, coma was seen in 10% of 1000 patients studied.[44] Catatonia was seen in 11% of patients from that study, and patients may suddenly withdraw from this state with agitation and violence. This cycle may repeat itself several times. Psychotic reactions to PCP were seen in 16% of patients, and include typical religious delusions and hearing voices telling the user to harm someone. The acute, confused state with PCP use was seen in 24% of users, and users can be disoriented, lack judgment and short-term memory, and have slurred speech. Violence and agitation seen in PCP "overdose" are legendary, and violent behavior is reported in up to 40% of users.[36] Patients appear to have superhuman strength, and reports of patients breaking police handcuffs and fracturing their forearms in the process exist.[36] The basis of these accounts is thought to be that PCP is a dissociative anesthetic and blocks normal pain feedback to the user. Thus, pain does not restrict their actions, and therefore none of the inhibition is experienced that one would normally feel with self-destructive behavior. A side effect of these actions is that patients may perform prolonged isometric exercises as they struggle with physical restraints for hours. This activity can cause muscle damage that may lead to rhabdomyolysis.

Medical complications primarily consist of mild hypertension, rhabdomyolysis, hyperthermia, and seizures. Hypertension that is seen with PCP use alone typically requires no treatment other than observation. Rhabdomyolysis with PCP use is diagnosed in standard fashion, with elevated serum creatine kinase (CK) and with urine testing positive for occult blood, and few red blood cells (RBCs) seen microscopically. Patients with evidence of rhabdomyolysis require observation and early, aggressive treatment for advancing CK levels or signs of renal impairment. Treatment is the same as that for rhabdomyolysis caused by other insults: IV fluids, diuretics, and alkalinization of the urine with IV bicarbonate. Hyperthermia in the setting of PCP use can occur, and should be treated with aggressive cooling measures. There are reports that haloperidol (Haldol) use in PCP overdose may trigger a syndrome similar to neuroleptic malignant syndrome,[45] and benzodiazepines should be considered for sedation to avoid this potential complication. Seizures also have been reported with PCP use and should be treated in the standard fashion with benzodiazepines.

Finally, the ED physician should be aware that urine drug screens are positive in only 80% of patients who are clinically

diagnosed with PCP ingestion.[36] Most authors recommend observation of patients with history of use but no significant complications (behavioral or medical) for at least four hours. Patients who do not develop further symptoms may be safely discharged with a responsible party. Follow-up for substance abuse treatment should be given. Any patient with significant behavioral or medical complications of PCP use should be admitted for further observation and treatment. The half-life of PCP can be greater than 72 hours in some patients, and no antidote exists for PCP overdose. Though some have tried ion trapping with ammonium chloride to remove excess drug, this treatment is no longer recommended due to lack of proven benefit and the high risk of renal and hepatic injury.[46]

Amphetamines and Designer Drugs

Amphetamines are a class of noncatecholamine drugs that act as strong CNS stimulants. Amphetamine is phenylisopropylamine (Benzedrine). Designer drugs are compounds that have been chemically altered for the express purpose of producing "new" drugs that still have abuse potential of the parent compound, but that are technically not illegal. Designer drugs became illegal under the Controlled Substances Analogue Enforcement Act in 1986. Designer drugs are included under this heading as many of them are derived from amphetamines. While designer drugs have no accepted medical uses, amphetamines have several. Although highly controversial, short-term (2-3 months) use of amphetamines for appetite suppression is still legal. Around 80% of the legal use of these drugs is for weight loss.[47] The most common, chronic use of amphetamines is for treatment of narcolepsy and attention deficit disorder. Unfortunately, legal prescriptions are a very common source of amphetamines, with up to 80% of legally produced pills being diverted to illicit use.[48]

Amphetamines are commonly abused in two settings: individuals seeking performance enhancement, and those who take the drug to "get high." Amphetamines are taken inappropriately in many settings for performance enhancement. This type of abuse usually involves oral doses taken by truck drivers, students studying for exams, and football players or other athletes desiring improved speed or weight loss. These people are at risk for consequences of impaired judgment and exhaustion that come with their abuse of the drug. Those taking amphetamines for the euphoric effects often use the IV route, but also can use commercially produced Benzedrine inhalers. Tolerance rapidly develops, and users must increase their doses accordingly. IV injection of amphetamines produce a feeling of power, hyperactivity, and heightened sexual awareness. Chronic IV users (termed "speed freaks") develop characteristic signs of abuse but exhibit no physical signs of addiction. Signs to watch for include: irritability; weight loss; mood swings; depression; irregular sleep; nasal congestion; social problems, including neglect of work, school, family, and friends; and poor judgement with money. Like with cocaine, addicts often binge (IV usage up to 10 times per day for up to 1 week) to avoid the crash associated with drug cessation. During this time the person rarely eats or sleeps and ignores normal body care. They may become paranoid to the point of psychosis, and often are unpredictably dangerous and violent during these times. After the binge, they often sleep for up to 48 hours, eat large amounts of food, and experience severe depression.

The chemical structure of amphetamines is similar to that of adrenaline. They act by increasing release and inhibiting reuptake of dopamine and serotonin in the CNS. Minor substitutions (methoxyl group to the 4-position) significantly alter its properties and intensify the hallucinogenic features. Some amphetamine derivatives with higher abuse potential include: methamphetamine, methcathinone (Cat), 2, 5-dimethoxy-4-methylamphetamine (STP), 3,4-methylenedioxymethamphetamine (MDMA), and 3, 4-methoxy-N-ethylamphetamine (MDEA). Clandestine laboratories easily can produce illegal amphetamines, and they have sprouted across the United States with the highest concentration in the Southwest. Estimates indicate the illegal methamphetamine production has become a significant industry in California.[49] Methamphetamine is the most commonly synthesized drug, and it easily can be produced from over-the-counter ephedrine.

Methamphetamine. Considered "poor man's cocaine," the DEA classes methamphetamine as one of the fastest growing drug threats in America today. It can be taken orally, injected, snorted, or smoked. While initially a drug of abuse in California, its use spread to other states in the 1980s. Currently, an estimated 9.4 million people (4.2% of the U.S. population) have tried methamphetamine in their lifetimes, compared to 3.8 million in 1994. Drug Abuse Warning Network (DAWN) data show that ED visits for methamphetamine-related episodes have more than tripled between 1991 and 1994, rising from 4900 to 17,700.[50] Likewise, the DEA reports seizing 973 kg of methamphetamine in 1990 and 2264 kg in 1999. Although many clandestine labs operating in the United States are producing methamphetamine, the DEA reports almost all "super labs" are located in California and that these labs produce 85% of the methamphetamine distributed in the United States.

Known as "Ice," "Crystal," or "Glass" because of the large crystals produced by ephedrine reduction, Ice has become a major problem in some areas of the United States. Ice is a very pure form (98-100%) of the drug, and is now more common than cocaine in Hawaii. Its high lasts longer than cocaine's, and while more expensive than crack, it is cheaper to produce. Ice is a very difficult drug for law enforcement officials to detect as it is odorless, colorless, tasteless, and easy to transport. Methcathinone ("Cat") is similar in appearance and effect to methamphetamine. Originally appearing in the Soviet Union in 1982, it also began to appear in the United States in 1991. It is reportedly easier to make than methamphetamine and more potent/addictive as well. Highs can last up to six days, and methcathinone recently has been classified as a Schedule I drug.

The effects of methamphetamine may last for 2-3 days, and many medical complications have been reported. Stroke, cardiac dysrhythmias, myocardial infarction, tremor, anxiety, insomnia, paranoia, malnutrition, pulmonary edema, and death all have

been reported.[47] Withdrawal symptoms include: abdominal pain, gastroenteritis, headache, lethargy, hunger, and depression sometimes leading to suicide. Stroke and cardiac complications seem more common in users who combine methamphetamine and alcohol. Pregnant women who abuse methamphetamine have similar risks as users of cocaine, and their children often experience intrauterine growth retardation, premature birth, and developmental and permanent cognitive disorders.[51] Reports of inadvertent pediatric poisonings with methamphetamine have been increasing. These are particularly dangerous, as one author points out, because these patients present with signs and symptoms of pediatric neurological or abdominal emergencies and may be misdiagnosed with these disorders.[52] Methamphetamine association with trauma also has been noted, with one study finding nearly a 50% increase in positive drug screens in their patients from 1989 to 1994.[53]

Club Drugs: MDMA and GHB. Club drugs refer to illicit drugs that have become popular in recent years as methods of enhancing club and rave experiences. Raves are dance parties where loud techno-music is played for extended periods of time. Raves have become popular both in the United States and Europe, with some rave parties having in excess of 20,000 people in attendance. Dancers take drugs such as MDMA, GHB, LSD, and ketamine ("Special K") alone or in combination and dance for hours at a time. Drugs often are sold openly at these parties, and users there often are unaware of the potentially serious side effects of their drug use. The primary dangers appear to be from hyperthermia and dehydration that can lead to heat stroke and rhabdomyolysis.[54] Two drugs, MDMA and GHB, commonly used at rave parties will be discussed.

MDMA. MDMA was one of the first designer drugs produced, and is known on the street as "Ecstasy," "XTC," and "Adam." MDMA can be found in capsule or pill forms (50-200 mg per dose), which are often adorned with bird motifs. The drug initially was developed in Germany in 1914 for the purpose of appetite suppression by E. Merck and Company, but was never made available to the public. It briefly was used by psychologists to facilitate psychotherapy, and became popular as a drug of abuse in the 1980s.[55] MDMAs use has dramatically increased in recent years. Estimates of lifetime use among college students range as high as 39%.[56] U.S. Customs reported seizing 400,000 tablets in 1997 and 8,000,000 in the first eight months of 2000 alone, but estimate 2 million tablets are smuggled into the United States each week. Popular in Europe before the United States, its use has increased there as well, with approximately 1 million tablets used in the United Kingdom each weekend. The majority of MDMA consumed in the United States (and the world) is produced in and imported from Belgium and the Netherlands. The profit margin for MDMA is enormous; tablets that cost less than $1 to produce can be sold for up to $40.[55] The 1998 NHSDA found that 1.5% of Americans age 12 and older had used MDMA at least once. Due to its popularity among adolescents and young adults at clubs, raves, and concerts, the most frequent use reported was 5.0% by those between ages 18 and 25.[2] Alarmingly, in 1999, 2.7% of 8th-graders reported lifetime use of MDMA, with 1.7% of them reporting use within the past year.[20]

Ingestion of MDMA produces peak plasma levels in 2-3 hours. In contrast to most other amphetamines, effects last only 4-6 hours. A typical dose ("hit") is 100 mg, but ranges from 50 mg to 250 mg. Lower doses of MDMA produce effects including heightened sexual experience, euphoria, verbosity, and sociability, in addition to enhanced hallucinogenic effects of intense color schemes and sensations.[35] Even lower doses can produce undesirable side effects including nausea, diaphoresis, anorexia, tremor, tics, paresthesias, tachycardia, urinary retention, and muscle aches. Bruxism, or jaw clenching, is seen in nearly 100% of MDMA users. They often resort to use of pacifiers or lollipops to relieve jaw tension. MDMAs reputation for enhanced sexual experiences perhaps is, ironically, based on sexual dysfunction induced by MDMA. In one survey, difficulty achieving orgasm was reported by 70% of males and 35% of females.[57]

Serious complications can follow MDMA use, including: fatal dysrhythmias, hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, acute renal failure, cerebral infarcts, hemorrhage, syncope, fulminant hepatic failure, seizures, coma, and death.[47] Dangerous complications of MDMA use can appear unpredictably within only a few hours after use, thus prompt recognition and treatment of these patients can be important. Two unusual complications related to MDMA use are hepatotoxicity and hyponatremia. The mechanism behind these complications is unknown. Liver damage can occur following single overdose or chronic use and can progress to hepatic failure and liver transplant.[58] Hyponatremia is seen in acute overdose, and serum sodium levels as low as 115 mEq/L have been reported.[59]

Some effects of MDMA use still are being elucidated, as a recent report found cardiac effects from MDMA were similar to dobutamine use.[60] They report MDMA had no ionotropic effects, but increased heart rate, blood pressure, and myocardial oxygen consumption in a similar fashion to dobutamine 20-40 mcg/kg/min IV. These emerging studies indicate that new problems with these more recently developed drugs may still appear. Likewise, chronic effects are not fully established either. Chronic MDMA use in animal studies demonstrate evidence of central serotinergic nerve terminal destruction.[61] Rapid tolerance to the psychoactive properties of MDMA occur within hours of repeated doses, while little tolerance develops with the less desirable effects of dysphoria, paranoia, and anxiety. Thus, users tend to self-limit use of MDMA and extended use has not been reported. While MDMA was classified as a Schedule I drug in 1985, a related compound, 3, 4-methylenedioxy-N-ethylamphetamine (MDEA, street name "Eve"), currently is not scheduled. Less is known about MDEA, but effects and complications appear to be similar.

GHB. Gamma-hydroxybutyrate (GHB) is a clear, colorless liquid that is similar in appearance to water. It was first synthesized in 1960, and was developed for use as an IV anesthetic. Its use was soon discontinued due to lack of analgesia and the potential for seizures. In the late 1980s, GHB became known as a "nutritional supplement" for body builders (thought to cause

increase in growth hormone levels) and dieters. It was sold over-the-counter in health food stores, gyms, and through mail-order sources. At the same time, it also became known for its euphoric and CNS depression effects and rapidly became a popular drug of abuse. In 1990 the FDA banned the sale and manufacture of GHB; in March of 2000 GHB was classed as a Schedule I drug.

Accurate statistics on GHB use are difficult to obtain. It does not show up on common drug screens, is commonly used with alcohol, and can have similar effects. Between 1995 and 1999, medical examiners reported 32 documented fatalities that were attributed to GHB abuse. Most of these deaths were in combination with alcohol, but eight of the 32 solely were attributed to GHB. DAWN data reports only 54 drug mentions for GHB in 1994, with reports rising to 764 in 1997.[50] GHB is produced in clandestine laboratories, and since 1997 the DEA reports 100 cases of illicit laboratories. GHB is sold on the street under the following names: Liquid X, Liquid Ecstasy, Growth Hormone X, Grievous Bodily Harm, Scoop, Water, Everclear, EZ Lay, and Georgia HomeBoy.

The primary users are teenagers and young adults who take the drug at bars, night clubs, raves, and gyms. GHB has become popular for abuse in three separate categories: recreational abuse for euphoria and alleged hallucinogenic effects, by bodybuilders who use it for alleged anabolic effects or as a sleep aid, and by individuals to aid in sexual assault as a "date rape" drug. Use of GHB for date rape is particularly disturbing. GHB is rapidly eliminated from the body, and therefore, difficult to detect. It's fast onset, CNS depression, and amnesic effects often render the victim unable to recall exact events surrounding the assault. The DEA reports 22 cases in which GHB specifically was used for sexual assault since 1996. Undoubtedly, more cases exist but are not reported or are impossible to substantiate.

GHB is easily made from its precursor gamma-butyrolactone (GBL), which is found in floor cleaning products, nail polish, and extra-strength adhesive (e.g., Super Glue) removers. Saponification of GBL with lye converts it to GHB with nearly 100% efficiency. Users also can bypass the chemical conversion, as the body converts GBL into GHB as well, producing the same symptoms as direct GHB ingestion. GBL is sold under the following names: Revivarant, Remforce, Firewater, Enliven, Revitalize Plus, Thunder Nectar, and G3 among others. GBL is a Scheduled drug in only a few states where GHB is federally a Schedule I drug. Case reports of abuse problems similar to GHB are beginning to be reported in the literature.[62,63]

GHB is absorbed rapidly after ingestion, and takes only 20-30 minutes to reach maximal plasma concentration. Elimination half-life is only 27 minutes, and is released via carbon dioxide from the lungs. GHB binds to GABA-β receptors in the brain, producing CNS depression. Supporting the bodybuilder's claim are several small studies in rats showing GHB does indeed raise growth hormone levels.[64] However, data demonstrating increased muscle mass in these lab animals is lacking. Clinically, the hallmark of GHB overdose is rapid and profound CNS depression. In lower doses (10-30 mg/kg) GHB can produce short-term amnesia, hypotonia, drowsiness, euphoria, ataxia, and dizziness. Higher doses (≥ 50 mg/kg) produce coma, bradycardia, apnea, Cheyne-Stokes respirations, vomiting, myoclonic seizures, and death. Other reported complications include hypotension, aspiration pneumonia, agitation, delirium, and loss of peripheral vision.[65] Key clues to intoxication with GHB include marked agitation with stimulation followed by apnea and hypoxia or abrupt, aggressive behavior with myoclonic seizures followed immediately by drowsiness and a comatose-like state.[66] Patients may tolerate oral intubation without additional anesthesia. Such deep levels of anesthesia typically last only 1-4 hours and spontaneously resolve with only supportive treatment. Patients can recover in only several minutes from deep anesthesia as well. A common scenario with GHB overdose is that emergency medical services workers will intubate an obtunded patient who suddenly awakens to self-extubate soon after arrival to the ED. Fortunately, the short half-life of GHB means that once the patient has awakened, he or she will not return to deep levels of anesthesia again. It is important to remember that many GHB users combine GHB and alcohol and that clinical effects of other coingestions may be delayed compared to GHB.

Treatment of patients known or suspected of GHB overdose is centered on respiratory support. Recently, one report suggested using physostigmine as a reversal agent for GHB overdose,[67] but further evaluation is needed to examine this treatment. Patients in whom significant coingestions have been ruled out, and who become awake and alert can be safely discharged with responsible parties after a short observation period. As GHB abuse is relatively new, it is not yet clear if psychological or physiological addictions occur. A recent case report demonstrating apparent GHB withdrawal suggests that physiological addiction is possible. The authors describe a withdrawal syndrome similar to alcohol withdrawal in a patient who used GHB daily for two and one-half years.[68] The severity of the withdrawal symptoms is underscored by the patients requirement for benzodiazepine sedation: 507 mg of lorazepam and 120 mg of diazepam over 90 hours.[175] No evidence of other drug abuse was found in this patient. Another author describes withdrawal symptoms in eight GHB abusers consisting of insomnia, anxiety, and tremor which persisted for 3-12 days.[69]

Methylphenidate (Ritalin). Ritalin is widely used in the treatment of attention deficit disorder and is produced only as a tablet. Ritalin abuse is becoming more popular among college-age students who use the drug to help stay awake to study for tests. Unique complications occur with Ritalin abuse when users crush tablets and attempt to snort or inject them IV. Intranasal use is less common than IV abuse, but also has led to fatalities.[70] Problems with IV use stem from the talc and cornstarch present in the oral tablets. Abusers will filter crushed tablets mixed with liquid through unsterilized cotton to remove these compounds, but this is not reliably effective. Respiratory complications are common as the lungs filter the talc and cornstarch which are still present. Talc emboli induce an inflammatory reaction in the arte-

Table 4. Accuracy of Urine Testing

DRUG	TIME DETECTABLE AFTER LAST USE
Marijuana — single use	1-7 days
Marijuana — chronic use	1-4 weeks
Cocaine	1-4 days
Heroin	1-4 days
Codeine	1-2 days
Morphine	1-3 days
Amphetamine	8-24 hours
Methamphetamine	1-2 days
Alcohol	1 day
Barbiturates	2-10 days
Benzodiazepines	2-7 days
Phencyclidine	1-7 days
LSD	8 hours
MDMA	Not detected
GHB	Not detected
Inhalants	Not detected

rioles that ultimately leads to occlusion of these small vessels and is followed by pulmonary hypertension. Precocious emphysema in IV abusers of Ritalin also has been reported.[71] As pulmonary vessels are occluded, it has been suggested that collateral vessels form and produce right-to-left shunting of blood. This shunted blood contains unfiltered talc and cornstarch, leading to systemic arteriole occlusion. Permanent visual loss from retinal arteriole occlusion and talc emboli in the brain have been reported.[72] Neck abscesses[73] and mycotic eye infections[74] also have been reported with IV Ritalin abuse.

Treatment and Withdrawal. Treatment of amphetamine abuse depends on the presenting symptoms. The most serious complications of hyperthermia, hypertension, seizures, cardiovascular instability, and self-inflicted trauma should be treated as follows. Patients with traumatic injuries should be treated under standard ATLS guidelines. After adequate airway control, seizures should be treated with IV diazepam followed by phenytoin for resistant cases. Haloperidol should be avoided in general, as at least one study found it increased the mania-like mood changes from MDMA.[75] Hypertension and tachycardia, if significant, may be treated with labetalol, or separately with alpha-blockers (phentolamine) for hypertension and beta-blockers (atenolol) for tachycardia. It is important to remember to use both alpha- and beta-blockers together to avoid unopposed alpha stimulation (and theoretically increased hypertension) with beta blockade alone. Hyperthermia should be treated with fluids and active cooling. As with malignant hyperthermia, dantrolene may be helpful.

Until the mid-1980s, it was thought that withdrawal from amphetamines did not occur. It was later shown that true addiction and withdrawal are possible, but that the manifestation of withdrawal primarily is psychological. Thus, abrupt withdrawal is not dangerous, only uncomfortable, and is never an excuse to prescribe additional drug. Like with cocaine, depletion of dopamine produces a hard "crash" and strong craving for more amphetamine. The crash is characterized by profound fatigue, depression, anxiety, increased appetite, and psychomotor retardation. Individuals in this phase reportedly often become suicidal, and additional doses of amphetamine completely resolve these symptoms. Again like cocaine, some withdrawal symptoms (mood swings, anxiety, depression, sleep disturbances, and low energy) may persist for months.

Drug-Seeking Patients

Patients who visit the ED for the express purpose of obtaining prescription drugs to abuse them are termed "drug-seekers." Drug-seekers can be classified into several categories: fraudulent patients seeking drugs of abuse, patients with under-treated severe pain, and psychiatric patients.[76] Patients with severe, chronic pain who are not being managed appropriately and psychiatric patients will not be discussed.

Drug-seeking patients who are looking for drugs of abuse exhibit several common themes. They have complaints of pain that cannot be quantified: toothache, back pain, headache, and abdominal pain. The only objective measure of pain is tachycardia, and that may be present from other drug use, such as cocaine. Patients often are impatient with ED waits, are quick to escalate behavior, and complain in hopes the ED physician will provide the drugs they seek just to get them out of the ED. These patients often are very knowledgeable of medical terms, describing in detail their L_4-L_5 disc herniations that have been confirmed with MRIs and myelograms. Some patients will carry their "scam" further by complaining of renal colic and pricking their finger to provide evidence of blood in their urine sample. The most extreme example encountered by the author is a patient who was known to have self-administered "caverject," a penile injection treatment for impotence, and present complaining of priapism. Patients also present with out-of-town addresses, stating they have lost their medications and "just need it to get through to their doctor's appointment next week."

It is important to state from the outset that pain medicine should not be withheld in the ED from patients when the diagnosis of drug-seeking behavior is suspected to avoid "punishing legitimate patients" who are in true need of pain control. Giving pain relief to patients while in the ED should not be viewed as "giving in." It is just not necessary to treat the patient with more potent medications than are deemed appropriate for their complaints. Likewise, one does not have to prescribe potential drugs of abuse to patients for home use/abuse where legitimate questions about the validity of their complaints exist. When prescribing medications, it is important for the physician to set limits on the number and types of drugs given and to stick to them when the patient returns again.

Drug Testing

Urine drug testing is a procedure commonly used in the ED, but its benefits and limitations should be well understood. Most screening tests are inexpensive immunoassays with rapid turn-

around times. The length of time that a particular drug can be detected in an individual's urine is dependent on many factors, including chronicity and the patient's medical problems. *(See Table 4.)* Physicians also must be cognizant of the causes of false-positive testing. Potential cross-reacting agents for marijuana include ibuprofen, naproxen, and fenoprofen. Dextromethorphan, chlorpromazine, and poppy seeds may represent false-positives with opiate urine drug screening. Chlorpromazine, thioridazine, meperidine, dextromethorphan, diphenhydramine, and doxylamine can cross-react as PCP metabolites. Amphetamine metabolites in urine drug results may be due to ephedrine, methylphenidate, phenylpropanolamine, and any weight-reducing or decongestant medication. High concentrations of desipramine and amantadine also can cause false-positive results in amphetamine testing.[77]

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Physician CME Questions

97. Which of the following is correct concerning sedative-hypnotics?
    A. Barbiturate overdose is relatively benign.
    B. Benzodiazepine overdose is extremely dangerous.
    C. Some benzodiazepines have half-lives of more than 100 hours.
    D. Flumazenil is indicated in every benzodiazepine overdose.
    E. Withdrawal from benzodiazepines produces symptoms similar to alcohol withdrawal.

98. Which of the following is *incorrect* concerning inhalant abuse?
    A. Inhalants are more commonly used by teenagers than adults.
    B. Sudden sniffing death refers to death by stroke resulting from inhalant abuse.
    C. At least one author suggests using beta-blockers instead of epinephrine in sudden sniffing death resuscitation.
    D. Frequency of inhalant abuse is increasing with time.

99. Concerning hallucinogen abuse, which of the following is correct?
    A. As users have gained experience with it, PCP is no longer considered a dangerous drug of abuse.
    B. Marijuana may produce respiratory conditions similar to those caused by tobacco use.
    C. Rhabdomyolysis is *not* associated with PCP abuse.
    D. Hallucinogen use in the 1990s has steadily decreased.

100. Treatment for PCP-induced rhabdomyolysis is the same as that for rhabdomyolysis which is caused by other insults: IV fluids, diuretics, and alkalinization of the urine with IV bicarbonate.
    A. True
    B. False

101. Club drugs:
    A. refer to "designer drugs," including GHB and MDMA.
    B. are widely popular at "rave dances."
    C. are much more dangerous than most users realize.
    D. can be fatal after first-time use.
    E. All of the above

102. Which of the following is true concerning methamphetamine abuse?
    A. It is not as popular now as it was in the 1960s.
    B. It produces effects similar to cocaine abuse.
    C. Methamphetamine cannot be smoked.
    D. Tolerance does not develop with repeated use.

103. Unique complications that occur with Ritalin abuse (via injection and inhalation) are represented by which of the following?
    A. Precocious emphysema
    B. Pulmonary hypertension
    C. Neck abscesses
    D. Retinal arteriole occlusion
    E. All of the above

104. In a urine drug test, potential cross-reacting agents for marijuana include which of the following?
    A. Ibuprofen
    B. Naproxen
    C. Fenoprofen
    D. All of the above

Correction

An incorrect dosage was listed on page 72 of the March 26, 2001 (vol. 22, no. 7), Emergency Medicine Reports *on urinary tract infections. The on-line versions of the article have been corrected as follows: the dosage for phenazopyridine should be — adults, 100 mg 2 tablets tid or 200 mg 1 tablet tid not to exceed two days of therapy; children ages 6-12, 12 mg/kg/d divided into tid dosing not to exceed two days of therapy. Readers referring to the print version of that article should note the correction.* ■

In Future Issues: Stress Fractures