Common Substances of Abuse

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Education Gaps

1. With almost a third of adolescents admitting to ever drinking alcohol, and 25% ever using an illicit drug, substance abuse has a significant health impact on the adolescent population.
2. Pediatricians should be knowledgeable about the common substances abused by adolescents to properly prevent, recognize, counsel, and treat both acute and chronic use.

Objectives

After completing this article, readers should be able to:

1. Describe the general epidemiology of substance abuse in adolescents.
2. Determine when/how to evaluate and interpret substance abuse with laboratory testing.
3. Describe the pathophysiology, symptoms, and treatment for common substances of abuse.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
CNS	central nervous system
GABA	γ-aminobutyric acid
GHB	γ-hydroxybutyrate
LSD	lysergic acid diethylamide
MDMA	3,4-methylenedioxymethamphetamine
NMDA	N-methyl-D-aspartate
NSDUH	National Survey on Drug Use and Health
OTC	over-the-counter
SBIRT	Screening for Substance Use, Brief Intervention, and/or Referral to Treatment
THC	tetrahydrocannabinol

Abstract

Adolescent substance abuse remains common, with almost a third of adolescents admitting to ethanol use, and a quarter admitting to illicit drug use. It is essential for pediatricians to regularly screen adolescent patients for substance use, because early initiation of drug use has been associated with physical, behavioral, and social health risks. Adolescents abuse what is common and readily available; this includes ethanol, over-the-counter products, marijuana, and inhalants. The most common and effective clinical treatments for significant toxicity from substances of abuse is symptomatic and supportive care including hemodynamic support, respiratory support, and sedation to control psychomotor agitation.

EPIDEMIOLOGY

The majority of adolescent substance abuse is initiated between 15 and 17 years of age, but can begin as early as age 10 years. (1) Initiation of substance abuse at an early age has been associated with long-term physical, behavioral, and social health risks including alcohol use and dependence, use of other substances (ie, marijuana, stimulants, and hallucinogens), school failure, high-risk sexual behaviors, and mental health disorders. (2)(3)(4)(5)(6)(7)(8)(9)(10)(11)(12) Poisonings and drug overdose is a leading cause of injury-related deaths in the adolescent population. (13) The death rate from drug overdose among adolescents aged 15 to 19 years more than doubled from 1999 (1.6 per 100,000) to 2007 (4.2 per 100,000). (14) Although there was a notable 26% decline from 2007 to 2014 (3.1 per 100,000), death rates from overdose increased in 2015 (3.7 per 100,000). In 2015, it was reported that most drug overdose deaths were unintentional, and rates were highest for opioids, specifically heroin. Early prevention, recognition, and intervention are critical in the adolescent age group.

Adolescents typically abuse what is inexpensive and readily available, such as alcohol, tobacco products, over-the-counter (OTC) pharmaceuticals, marijuana, and inhalants. Alcohol (ethanol) continues to be the most commonly abused substance. According to the 2015 National Survey on Drug Use and Health (NSDUH), 28.4% of youths aged 12 to 17 years ever drank alcohol and 5.8% reported binge drinking in the past month. (15) Twenty-five percent of adolescents admitted to ever using an illicit drug, and 8.8% used in the past month. The most common illicit drug was marijuana (12.6% in past year), followed by inhalants (9.1%) and hallucinogens (3.1%). A smaller number of adolescents admit to nonmedical use of prescription medications (2%). The Monitoring the Future survey reports that overall drug use, as well as alcohol and tobacco use, have slightly decreased since 2014. (16) However, hallucinogen abuse has remained steady, while abuse of cough and cold medication and novel drugs of abuse, such as synthetic stimulants and canthinones, has increased.

ROLE OF PRIMARY CARE CLINICIANS

The American Academy of Pediatrics (AAP) recommends an annual tobacco, alcohol, and drug use assessment beginning at the 11-year-old health supervision visit. (17) Research has demonstrated that many adolescents do not discuss substance abuse with their physicians because they are not asked, despite a desire to disclose. (18)(19)(20)(21) Emphasis should be placed on confidentiality, which will result in greater disclosure. When evaluating substance abuse, pediatricians should ask about nonmedical use of all categories of drugs: alcohol, nicotine, OTC and prescription medications, and illicit/recreational drugs (both common and novel). They should ask about frequency and routes of exposure (ingestion, injection, etc), which may reflect the magnitude of drug use. Primary care physicians should also inquire about caregiver knowledge of their drug use. This may reveal more information about the living and social environment that may need further investigation.

Several screening tools are available to help identify and stratify the risks of substance abuse. (22)(23)(24)(25)(26)(27) The AAP recommends the Screening for Substance Use, Brief Intervention, and/or Referral to Treatment (SBIRT) guidelines, which were designed by the US Substance Abuse and Mental Health Services Administration. In addition to SBIRT, the Society of Adolescent Health and Medicine has recommended several other tools that can be used to screen for various kinds of substance abuse focused at different age groups. Examples include the Alcohol Use Disorders Identification Test, Drug Abuse Screen Test screening tool, and the "Car, Relax, Alone, Forgotten, Family/friend, Trouble." (25) These screening tools have questions evaluating and qualifying risk factors associated with drug use: age at first use, frequency/pattern of use, and impact and consequences on physical, emotional, and social well-being. *The Diagnostic and Statistical Manual of Mental Disorders, 5th edition* describes a spectrum of abuse/dependence: experimentation, nonproblematic or problematic use, abuse, and dependence. (28)(29) All of these factors will help determine the degree of concern and amount of intervention that is needed: counseling and close follow-up in the primary care setting or referral to an addiction/drug rehabilitation specialist.

LABORATORY EVALUATION

Laboratory evaluation for substance abuse, such as urinary drug immunoassays, can provide ancillary information to a complete and thorough physical and mental health evaluation. Drug assays can help confirm, exclude, and/or specify systemic drug exposure. However, caution should be used when interpreting results. Standard urine drug screens have not been shown to change management in the emergency department or add any further information when obtaining a drug use history. (30)(31)(32) Obtaining a thorough confidential history and physician examination can provide great detail on acute and chronic substance use (Table 1).

Urine drug immunoassays are common qualitative tests for drug exposure. They are inexpensive, noninvasive, and

TABLE 1. **Substances of Abuse and Associated Clinical Symptoms**

	CLINICAL SYMPTOMS			
DRUG CATEGORY	**CARDIOVASCULAR**	**NERVOUS SYSTEM**	**GASTROINTESTINAL**	**OTHER**
Ethanol	Tachycardia or bradycardia, hypotension	Miosis, ataxia, agitation, sedation, coma	Pain, nausea, vomiting	Respiratory depression, hypoglycemia (young children)
Nicotine	Tachycardia and Hypertension (early), Bradycardia and Hypotension (late)	Seizures, sedation, coma, weakness/paralysis	Nausea, vomiting	
Marijuana	Tachycardia, hypertension	Agitation, sedation, psychosis	Pain, nausea, vomiting	
Antihistamines	Tachycardia, hypertension	Agitation, delirium, sedation, mydriasis, hallucinations	Decreased bowel sounds	Flushed, dry skin and mucous membranes, urinary retention, hyperthermia
Dextromethorphan	Tachycardia, hypertension, flushed	Agitation, delirium, sedation, mydriasis or miosis, ataxia, nystagmus, hyperreflexia, hallucinations		Hyperthermia
Inhalants	Tachycardia, dysrhythmia (rare)	Euphoria, sedation		Angioedema
Sedative hypnotics	Bradycardia, hypotension	Sedation, coma, ataxia, nystagmus		Respiratory depression
Hallucinogens	Tachycardia, hypertension	Euphoria, auditory and visual hallucinations, nystagmus, ataxia, psychosis, mydriasis, coma		Hyperthermia
Stimulants/ sympathomimetics	Tachycardia, hypertension	Agitation, psychosis, mydriasis	Nausea, vomiting, diarrhea	Hyperthermia, diaphoresis
Opioids/opiates	Bradycardia, hypotension	Euphoria, sedation, coma	Ileus	Respiratory depression

rapid. However, determination of exact timeline, route of exposure, and level of intoxication is difficult with urine immunoassays. Each category of drug has variable durations of detection after exposure, and has potential false-positive and -negative results (Table 2). (32)(33)(34) Common adulterants to avoid drug detection include addition of water (dilution), using another subject's urine sample, ingestion of diuretics or overconsumption of water (dilution), household chemicals, salt, and oxidants. (35)

Hair follicle testing is an additional noninvasive modality to detect drug exposure. Hair testing can evaluate for subacute or chronic exposure (typically weeks to 2–3 months earlier). However, it can be prone to external contamination and is dependent on an adequate hair sample (length) and proper sample preparation. Detection of drug metabolites can aid in distinguishing between a systemic exposure and external contamination. Like urine, hair testing is difficult to clinically correlate with the level of intoxication, exact timing, and route of exposure. The color of the subject's hair may also be a variable in the accuracy of results. (36)(37)(38)

Blood (whole, serum, plasma) testing is a more accurate modality for detecting systemic exposure and can make a better clinical correlation with the level of intoxication. However, this modality is invasive, often expensive, and generally can take several days to weeks for results, which limits its clinical usefulness for acute patient care.

Regardless of the sampling source, confirmatory testing should be considered when results of initial screening tests are unexpected, concerns for false-positive or -negative results exist, or specific compounds/drugs need to be identified. Biologic samples from the earliest time of symptom onset or suspected toxicity provide the best opportunity to clinically correlate intoxication and detect an exposure. The modality for confirmatory testing is typically either gas or high-performance liquid chromatography paired with mass spectroscopy. Results are quantitative rather than qualitative, and testing can be performed for specific

TABLE 2. **Common Drug Classes Found in Urine Drug Screening Immunoassays and Testing Characteristics**

URINE DRUG SCREENING CATEGORIES	DURATION OF DETECTION[a]	FALSE POSITIVES AND NEGATIVES[b]
Amphetamines	1-4 days	Can cross-react with decongestants, ADHD medications, Methamphetamines, MDMA, ephedrine, bupropion
Barbiturates	1-4 days	Phenobarbital can be detected for 3–4 weeks
Benzodiazepines	1-4 days	Can have false negatives for lorazepam, alprazolam, midazolam, and clonazepam. Diazepam can be detected for 3–4 weeks
Cocaine (benzoylecgonine)	2-4 days	Do not commonly occur
Opiates	1-4 days	False negatives can occur with synthetic and semi-synthetic opioids (oxycodone, hydromorphone, fentanyl, etc.)
Phencyclidine	1-8 days	Can cross-react with ketamine, dextromethorphan, diphenhydramine.
Marijuana (THC metabolites)	7-30 days	Reported false positives include dronabinol, efavirenz, proton pump inhibitors, nonsteroidal anti-inflammatory drugs

ADHD=attention-deficit/hyperactivity disorder; MDMA=3,4-methylenedioxymethamphetamine; THC=tetrahydrocannabinol.
[a]*Detection period varies and depends on chronicity of exposure.*
[b]*This is not an all-inclusive list of potential false positives/cross reactants and false negatives.*

substances rather than drug categories. The disadvantage of this modality is cost and significant delays in obtaining results.

COMMON SUBSTANCES OF ABUSE

Alcohol (Ethanol)

Over a quarter of adolescents admit to ever drinking alcohol, with almost 6% admitting to binge drinking in the past month. (15) Ingestion is the most common route of exposure for ethanol; however, there are reports of inhalation (vaporization) and exposure via other orifices (vaginal suppositories, rectal administration). (39)(40) Common household items may also contain high concentrations of ethanol including tinctures and essential oils, cosmetics, mouthwashes, rubbing alcohol, hand sanitizers, and cooking extracts (eg, vanilla). Ethanol is also limitedly available as a powder that can be reconstituted as a solution. (41)

Absorption of alcohol after ingestion is typically rapid and onset of intoxication is relatively quick in a naive user. (42)(43) Alcohol enhances the inhibitory effects of γ-aminobutyric acid (GABA) at the GABA-A receptor, while blocking the N-methyl-D-aspartate (NMDA) subtype of glutamate, an excitatory amino acid receptor. Intoxication can be more severe when coingested with other sedative-hypnotics. The potential blood ethanol concentration can be roughly estimated if a dose of ethanol is known. For a 60-kg patient (estimated total body water [60%] or volume of distribution [V_d] = 36 L) who ingested 4 "shots" of 40% ethanol solution, calculation is as follows:

$$1 \text{ shot} = 30 \text{ mL}, \ 4 \text{ shots} = 120 \text{ mL}$$

$$120 \text{ mL} \times 40\% = 48 \text{ mL of } 100\% \text{ ethanol}$$

$$48 \text{ mL} \times 0.79 \text{ (specific gravity of ethanol)} = 37.9 \text{ g or } 37,900 \textit{ mg of ethanol}$$

$$37{,}900 \text{ mg} / 36 \text{ L} = 1{,}053 \text{ mg/L} = 105 \text{ mg/dL}$$

Many naive users can have signs of intoxication with blood concentrations as low as 20 to 60 mg/dL. The rate of metabolic degradation is constant, typically 20 mg/dL per hour. (42)(43) Severe complications occur after a significant ingestion or coingestion of other sedatives, and can lead to respiratory depression, vomiting with aspiration, or trauma. It is important to obtain a history again and repeat the physical examination after an intoxicated patient becomes sober (regardless of the ingestion or drug) to evaluate for trauma, coingestants, and other medical diagnoses. Urinary ethanol may detect exposure, but is prone to contamination and is difficult to clinically correlate. Breath ethanol detectors estimate blood ethanol concentration but is dependent on the exhalation effort of the subject, and can have a falsely elevated or low values because of many complicating factors.

(44) If accurate knowledge of ethanol exposure is needed, blood (serum) ethanol concentration is recommended.

Tobacco/Nicotine

Nicotine is derived from members of the genus *Nicotiana* plant. Exposure is commonly via inhaled (smoke, vaporized), oral (chew, gum, lozenges), and dermal (patches) routes. Initiation of tobacco use at a young age is concerning for the potential long-term health risks of chronic exposure: lung disease, cardiovascular complications, and cancers. In 2016, 20.2% of high school students admitted to using any tobacco product in the past 30 days. There have been recent declines in cigarette specific use trends. In 2016, 8 (8%) of 100 high school students reported smoking cigarettes in the past 30 days, a decrease from 15.8% in 2011. (15) In contrast, use of electronic cigarettes is increasing: in 2016, 11 (11.3%) of 100 high school students reported using electronic cigarettes in the past 30 days, increased from 1.5% in 2011. Although the long-term effects of inhaling vapor from electronic cigarettes are not known, it has been demonstrated to contain toxicants including heavy metals, formaldehyde, acetaldehyde, and acetone. (45)(46) The amount of nicotine absorbed through smoking is highly variable, depending on the product and the user. Cigars, pipes, and concentrated vaporization products typically have higher nicotine content than traditional cigarettes.

Nicotine binds to central nicotinic receptors and directly stimulates neurotransmitter release including dopamine, glutamine, norepinephrine, acetylcholine, GABA, serotonin, and endorphins. Low-dose exposures result in sympathomimetic agonism and symptoms include nausea/vomiting, tachycardia, hyperalert state, hypertension, and euphoria. With larger-dose exposures, parasympathetic and neuromuscular-blocking effects may be more prominent including central nervous system (CNS) depression, seizures, and paralysis. There is no specific treatment for nicotine toxicity besides symptomatic and supportive care. Confirmation of exposure can be sent for its metabolite, cotinine.

Marijuana/Cannabis

Marijuana is the illicit substance most abused by adolescents. (15) National surveys do not show any recent trends indicating increased abuse, but adolescent perception on risk of marijuana use to health continues to decline. (16) Marijuana contains several cannabinoids; tetrahydrocannabinol (THC) is the most psychoactive and responsible for most of the clinical effects. Most common routes of exposure are inhalation (smoke, vaporization) and ingestion (THC-infused food products). Onset of symptoms after inhalation is typically rapid with peak effects seen after only a few minutes. (47) Ingestion of marijuana can lead to delayed and prolonged effects, which can peak at 2 to 4 hours and last up to 8 hours. THC and other cannabinoids are agonists at the CB1 and CB2 receptor, which can be found in the central and peripheral nervous system and the immune system. Symptoms after marijuana use can be quite variable: sedation, ataxia, psychosis, anxiety, delirium, vomiting, and tachycardia. Highly concentrated inhaled products (waxes, dabs, budders) and edible products can contain high amounts of THC. These higher potency products can lead to more significant symptoms such as psychosis, anxiety, and agitation. (48)(49) Chronic marijuana use in adolescents has been associated with poor academic performance (including less likely to graduate high school), adulthood psychotic disorders and symptoms, and other illicit drug use and drug addiction. (50)(51)(52)(53)(54)(55)(56)(57)(58)(59)(60)(61)(62)

Short-acting benzodiazepines or antipsychotics can be helpful in controlling more severe behavioral and psychomotor symptoms. Cannabis hyperemesis syndrome is a clinical syndrome that has been described after chronic inhalational use. Symptoms include severe abdominal pain, vomiting, and nausea often relieved by hot bathing. (63)(64)(65)(66)(67)(68)(69)(70)(71) Standard treatment consists of intravenous fluid hydration, antiemetics, and benzodiazepines. Haloperidol and capsaicin cream has been shown to be most effective in case reports. (63)(64)(65)(66)(67)(68)(69)(70)(71)

Standard urine drug immunoassays are qualitative assays that detect THC metabolites, usually at the cutoff value of 50 ng/mL. They can be positive up to a week after acute use and several weeks after chronic use. Although contact "highs" can occur after passive smoke exposure, positive screening results after passive smoke exposure are rare and only reported in small, confined, and unventilated environments with large amounts of smoke. (72)(73)(74)(75)(76)(77) Synthetic cannabinoids, such as "k2" and "spice," have chemical structures different from THC. Thus, use of these products will not result in a positive THC/marijuana finding on a standard urine drug immunoassay.

OTC MEDICATIONS

OTC medications are often abused by adolescents because they are inexpensive and readily available. The most common class abused by adolescents includes ingredients of the cough-and-cold category of OTC medications. (78)(79)(80)(81)(82)(83)(84)(85)(86) Active ingredients include antihistamines (diphenhydramine, chlorpheniramine), cough suppressants (dextromethorphan), and decongestants (pseudoephedrine, phenylephrine). Antihistamines are also found in many OTC sleep aids and allergy medications.

Antihistamine ingestions typically lead to sedation but can result in antimuscarinic toxicity (dry mouth, blurred vision, photophobia, tachycardia, urinary retention, hyperthermia, mental confusion) by antagonism at the histamine (H1) receptors (Table 1). Rarely, diphenhydramine can have cardiotoxicity from blocking sodium channels, which results in QRS interval widening, and dysrhythmias. Deaths have been reported from significant overdoses. (87)(88)

Dextromethorphan is an isomer of a potent μ-agonist levorphanol. Common slang terms for dextromethorphan abuse includes "dexing, robo-tripping, triple Cs." Dextromethorphan agonism at opioid/μ receptors is weak but it is the mechanism for its therapeutic use as a cough suppressant. Dextromethorphan also has NMDA-receptor antagonism, which leads to the more common clinical sequelae in the setting of misuse and abuse. Physical examination findings of dextromethorphan intoxication include mydriasis or miosis, nystagmus, CNS depression, tachycardia, delirium/agitation, slurred speech, hyperreflexia, and visual hallucinations. (81)(85)(89)(90)(91)(92) Opioid toxidrome is not commonly encountered. Serotonergic effects, including altered mental status, hyperreflexia, and autonomic instability (hyperthermia, tachycardia, hypertension), can be seen in the setting of a large overdose or when ingested with other serotonergic xenobiotics. (93)

Pseudoephedrine and phenylephrine are both sympathomimetic and can lead to a hyperadrenergic state. Symptoms of sympathomimetic toxicity include agitation, hyperthermia, tachycardia, and hypertension. Typically, the amounts of these medications in OTC products are low and significant toxicity is rare.

Treatment for toxicity from any of these OTC cough and cold medication ingredients include control of psychomotor agitation, delirium, and seizures. Benzodiazepines, such as lorazepam, are first-line therapy. Physostigmine, an acetylcholinesterase inhibitor, can be considered to reverse antimuscarinic toxidrome from antihistamines. (94)(95)(96)(97)(98)(99)(100)(101)(102)(103) In a retrospective review, it was shown to be more effective in controlling agitation and reversing delirium than benzodiazepines. (102) However, reversal of antimuscarinic toxicity is short acting (15–45 minutes) and should not be used in patients with asthma, cardiotoxicity, or seizures. (103)(104) Physostigmine infusion has been used safely and effectively for patients with prolonged and persistent antimuscarinic effects. (105)(106) Sodium bicarbonate or acetate intravenous bolus infusions (1–2 mEq/kg) can be used to overcome sodium channel blockade in the setting of severe diphenhydramine cardiotoxicity. In the rare circumstance of hypertensive emergency resulting from sympathomimetics, direct vasodilators, including nitroprusside, and phentolamine can be beneficial. Acetaminophen is a common coingredient in OTC cough and cold products; patients should always be evaluated for potential toxicity by obtaining the acetaminophen concentration. (107)(108) Although not specifically detected on standard urine drug immunoassays, diphenhydramine commonly cross-reacts with the tricyclic antidepressant urine immunoassay, and both dextromethorphan and diphenhydramine cross-react with the phencyclidine immunoassay.

INHALANTS

Abuse of inhalants remains popular among adolescents and an estimated 9% of the US population 12 years and older have abused or misused an inhalant for psychoactive properties, more than any other age group. (15) Other terms for inhalation include "huffing," "bagging," and "dusting." Most inhalants are organic compounds containing hydrogen and carbon, or hydrocarbons. They are commonly used as solvents and diluents in many various household products including cleaners, aerosols, fuels, and essential oils. Hydrocarbons can be aliphatic or aromatic and may also contain halogens (bromide, fluoride, etc). Nitrous oxide is also abused as an inhalant and found as a propellant in products such as whipped cream.

After inhalation, onset of psychoactive effects is rapid. Hydrocarbons diffuse through the pulmonary system and readily cross the blood-brain barrier and affect neurotransmitters, which include glutamate/NMDA, GABA, dopamine, and opioid receptors. (109)(110) Symptoms can include CNS depression, euphoria, and tachycardia. Recreational use of inhalants has a short duration of effect. A rare complication is angioedema. (111) Chronic use of toluene can lead to renal tubular acidosis and resulting severe hypokalemia. (112)(113) It is postulated that hydrocarbons, specifically halogenated hydrocarbons, may sensitize the myocardium to catecholamines by inhibiting calcium signaling which may lead to cardiac dysrhythmias. (114) Chronic hydrocarbon inhalant abuse can lead to severe abnormalities of the nervous system, including neuropathies, neuropsychiatric disorders, encephalopathy, and dementia. (115)

Intoxication from acute inhalant abuse typically has rapid resolution of symptoms and medical treatment is often unnecessary. Prolonged hospital admission with potassium repletion may be necessary in the setting of renal tubular acidosis from toluene because of the significant weakness that may develop. Cardiac dysrhythmias should be treated with standard resuscitative measures. Catecholamines should be used cautiously because of the theoretical risk of worsening sensitized myocardium. Urine assays are available to detect urinary metabolites of specific hydrocarbons.

SEDATIVE-HYPNOTICS

Sedative-hypnotics include a diverse class of drugs and medications and are rarely abused by adolescents (estimated 23,000 or 0.1%). (15) Benzodiazepines are agonists at the GABA-A receptor and each individual benzodiazepine has varying time to onset and duration of action. Barbiturates are also agonists at the GABA-A receptor but may lead to more significant symptoms than benzodiazepines. γ-hydroxybutyrate (GHB) is an agonist at the GABA-B receptor and is medically used for narcolepsy to induce sleep. It is abused as a sedative and for body building (mechanism is a purported increase in deep sleep, resulting in increased growth hormones). GHB is known to cause a deep but short-lived coma. γ-butyrolactone and 1,4-butanediol are related to GHB and can lead to similar toxicity. Other sedative-hypnotics that are no longer commonly abused include chloral hydrate (when used with ethanol called "Mickey Finn"), methaqualone ("qualudes"), carisoprodol ("soma coma"), baclofen, and meprobamate.

Regardless of the sedative-hypnotic, common symptoms of abuse and overdose are CNS depression, nystagmus, and ataxia. Respiratory depression and hypotension can occur in large oral overdose, intravenous use, or coingestion with other sedative-hypnotics. Flumazenil is a benzodiazepine receptor antagonist that can be given to reverse the toxicity of benzodiazepine toxicity. However, flumazenil should be used sparingly because it can precipitate withdrawal and seizures with chronic use. (115)(116)(117) Life-threatening withdrawal from most sedative-hypnotics can occur with abrupt cessation after chronic use and can be associated with agitation, hallucinations, tachycardia, and seizures. Standard urine drug immunoassays for benzodiazepines can be misleading, because they test for the common metabolite of select benzodiazepines: diazepam, chlordiazepoxide, clorazepate, and temazepam. These metabolites do not occur in the metabolism of commonly used benzodiazepines, including lorazepam, clonazepam, midazolam, and alprazolam, and result in false negatives.

HALLUCINOGENS

Hallucinogens are a diverse group of substances that alter and distort perception, thought processes, and mood. In 2016, the NSDUH reported that 1.4 million Americans older than 12 years were current users of hallucinogens (15). Several hallucinogens are commonly abused. The synthetic lysergamide, LSD, is derived from an ergot alkaloid of the fungus, *Claviceps purpurea,* and is a water-soluble, colorless, tasteless, and odorless powder. Mescaline is a naturally occurring hallucinogen found in peyote (*Lophophora williamsii*), a small blue-green spineless cactus found throughout the southwestern United States and northern Mexico. Peyote buttons are the round, fleshy tops of the cactus that can be removed, dried, and eaten. Six to twelve peyote buttons, or 270 to 540 mg of mescaline, are routinely required to produce hallucinogenic effects. (118) The onset of hallucinations begins 1 to 3 hours after ingestion and can last for up to 12 hours. (119) *Psilocybe* mushrooms contain the hallucinogen psilocybin. Ingestion of at least 5 g of psilocybin-containing mushrooms may be required to produce hallucinogenic effects, which are typically shorter in duration (4 hours). (120) *Salvia divinorum* is an herb and its use results in vivid hallucinations and synesthesia as well as diuresis, nausea, and dysphoria. (121) Recreational nutmeg use results in euphoria and hallucinations as well as nausea, vomiting, dizziness, flushing, tachycardia, and hypotension.

Physiologic abnormalities typically precede the perceptual changes and hallucinations (auditory and visual) induced by lysergamides. Sympathomimetic effects are common and dysphoria may compel patients to react to stimuli with unpredictable and aggressive behaviors. (122) Potentially life-threatening complications, such as hyperthermia, coma, respiratory arrest, hypertension, tachycardia, and coagulopathy, were described in 8 patients with a massive LSD overdose. (123) Serotonin toxicity could theoretically occur after the use of hallucinogens or with the use of other serotonergic medications such as serotonin-reuptake inhibitors. (124)(125) The vast majority of morbidity from hallucinogen use stems from secondary trauma that patients sustain while intoxicated and unaware of their surroundings.

Most hallucinogen users rarely seek medical attention because they experience only the desired effect of the drug and rarely produce life-threatening toxicity. There should be minimal external stimulation to prevent further agitation, and benzodiazepines can be used to treat psychomotor agitation. Morbidity and mortality can occur secondary to hyperthermia, rhabdomyolysis, hepatic necrosis, and disseminated intravascular coagulopathy. Physical restraint (without chemical restraint) should be avoided to prevent hyperthermia and rhabdomyolysis. Treatment of serotonin toxicity is largely supportive and requires avoidance of further exposure to serotonergic substances and medications. Specific therapy with agents like cyproheptadine has been used. (126) Long-term consequences of chronic LSD use include prolonged psychotic reactions, severe depression, exacerbation of preexisting psychiatric illness, and hallucinogen persisting perception disorder. (127)

While hallucinogens such as LSD can be detected on urine immunoassay, confirmation using high-performance

liquid chromatography or gas chromatography is necessary for most other hallucinogens. False-positive results on urine immunoassay for LSD are reported after exposure to several medications, including fentanyl, sertraline, haloperidol, or verapamil. (128)(129)

STIMULANTS/SYMPATHOMIMETICS

According to NSDUH, about 92,000 (0.4%) adolescents aged 12 to 17 years of age were current misusers of stimulants. (15) Stimulants include various substances including amphetamines (OTC, prescription, illicit), 3,4-methylenedioxymethamphetamine (MDMA), methylxanthines, and cocaine.

Amphetamines (Including Methamphetamines, MDMA)

Amphetamines represent a group of compounds with a common structure known as phenylethylamines. The pharmacologic effects of amphetamines are diverse, with their primary mechanism of action being the release of catecholamines, particularly dopamine, norepinephrine, and serotonin from presynaptic terminals and resulting in a hyperadrenergic state. Sympathomimetic effects are the most prominent clinical sequelae. (130)(131)(132) Life-threatening complications include intracerebral hemorrhage, stroke, seizures, myocardial infarction, ischemic colitis, obstetric complications, and dysrhythmias. (129)(130)(131)(132)(133) Without rapidly reversing the systemic signs and symptoms, multisystem organ failure and death may occur.

Evaluation of core body temperature is essential to diagnose the presence and degree of hyperthermia, which is a frequent and rapidly fatal manifestation in patients after significant amphetamine exposure. (134) Significant hyperthermia requires immediate and aggressive interventions to achieve rapid cooling. (135)(136)(137)(138) Benzodiazepines are effective for the treatment of psychomotor agitation induced by acute amphetamine overdose, and sedation should be titrated rapidly until the patient is calm. Physical restraints should be removed as soon as possible to prevent rhabdomyolysis and further heat generation. For seizures, benzodiazepines are also first-line therapy, followed by barbiturates or propofol. Dopamine antagonists such as haloperidol, droperidol, and olanzapine are options for amphetamine-induced delirium.

Qualitative urine immunoassays are available for amphetamines; however, false-positive and negative results are common (Table 2). Confirmatory testing is recommended to identify specific amphetamine compounds. Even with confirmatory testing, misidentification of isomeric substances such as L-methamphetamine (decongestant) with d-methamphetamine (illicit drug) can occur. (139)

3,4-Methylenedioxymethamphetamine

MDMA is also known as "ecstasy," "E," "Adam," "XTC," "molly," and "MDM." (137)(138)(139) Analogs exist that produce similar clinical effects, including 3,4-methylenedioxy-N-ethyamphetamine (MDEA or "Eve"), 3,4-methylenedioxyamphetamine (MDA or "love drug"), and paramethoxyamphetamine. MDMA is available in a range of doses (50–200 mg) in colorful and branded tablets and has a higher affinity for serotonin transporters (~10 times greater) than for dopamine and norepinephrine transporters. MDMA and similar analogs are so-called "entactogens" and are capable of producing euphoria, inner peace, and a desire to socialize. (140)(141)(142)(143)(144) People who use MDMA report that it enhances pleasure, heightens sexuality, and expands consciousness without the loss of control. Negative effects reported with acute use included ataxia, restlessness, confusion, poor concentration, and impaired memory. Significant free water intake combined with sodium loss from physical exertion in dance clubs may exacerbate the development of hyponatremia and cerebral edema. The use of "Molly" as well as "Molly" overdose has been associated with intracranial hemorrhage. (145 Chronic MDMA use has been associated with sleep and behavioral health disturbances, impulsiveness, and memory deficits). (146)

Methylxanthines (Caffeine, Theophylline, Theobromine)

Caffeine is the most assessable methylxanthine found in many beverages and in powdered form. Methylxanthines cause the release of endogenous catecholamines with stimulation of β 1 and β 2 receptors and act pharmacologically as adenosine receptor antagonists. (147) Adenosine antagonism leads to the release of norepinephrine and epinephrine. Methylxanthines also inhibit phosphodiesterase, the enzyme responsible for degradation of intracellular cyclic AMP, which has many effects, including an increase in intracellular calcium concentrations.

In adults, caffeine doses of 50 to 200 mg result in increased alertness, decreased drowsiness, and lessened fatigue, and caffeine doses of 200 to 500 mg produce adverse effects such as tremor, anxiety, diaphoresis, and palpitations. Most significant acute overdoses result in severe, protracted emesis, palpitations, tachycardia, and chest pain. Although sinus tachycardia is the most common finding, tachydysrhythmias including supraventricular tachycardia, multifocal atrial tachycardia, atrial fibrillation, premature ventricular contractions, and ventricular tachycardia have been reported. (148) Clinically significant dysrhythmias occur in 35% of patients with chronic theophylline poisoning but in only 10% of acute poisoning cases. (149) Ventricular dysrhythmias may occur at serum concentrations of 40 to 80 μg/mL in patients with chronic theophylline overdoses and at serum concentrations greater than 80 μg/mL

in patients with acute overdoses. Complications of vasoconstriction may occur including myocardial ischemia/infarction and cerebral vasoconstriction/stroke. (150)(151)(152) Caffeine promotes and prolongs seizures as adenosine antagonism lowers the seizure threshold. (153)(154) Skeletal muscle excitation, which may include tremor, fasciculation, hypertonicity, myoclonus, or even rhabdomyolysis, can occur. (155)(156)(157)(158) Severe hypokalemia, hypomagnesemia, and hypophosphatemia may also result, similar to toxicity from other β-agonists. (159)(160)(161)(162)

Electrocardiography and serum electrolyte measurement are recommended in the evaluation for methylxanthine toxicity. Multiple-dose activated charcoal is effective in enhancing the elimination of caffeine but may be difficult to administer due to nausea. Otherwise supportive care including antiemetics, electrolyte repletion (hypokalemia), and fluid resuscitation is recommended. α-adrenergic agonists (phenylephrine or norepinephrine) are effective vasopressors. In rare cases of refractory hypotension, the administration of an adrenergic antagonist may reverse β2 adrenergic–mediated vasodilation. Propranolol, esmolol, and metoprolol have been used successfully to treat methylxanthine-induced hypotension. (163)(164) Because of the antagonist effects at the adenosine receptor, administration of adenosine may not convert a methylxanthine-induced supraventricular tachycardia. Benzodiazepines may help in both CNS and cardiovascular effects by abating CNS stimulation and releasing catecholamines. Seizures not controlled with 1 or 2 therapeutic doses of a benzodiazepine should be treated with a barbiturate or propofol. Charcoal hemoperfusion was once considered the most effective method of enhanced elimination of methylxanthines, decreasing the half-life to 2 hours and increasing its clearance up to 6-fold. (165)(166)(167)(168) However, with the relative unavailability of this modality, hemodialysis is an excellent therapy. (169) Indications for hemodialysis therapy include clinically significant exposure with a serum theophylline or caffeine concentration greater than 90 μg/mL and symptoms, regardless of clinical stability and chronic theophylline poisoning associated with a serum theophylline concentration above 40 to 60 μg/mL or with a deteriorating clinical status.

Cocaine

Cocaine is contained in the leaves of *Erythroxylum coca*, a shrub found in Colombia, Peru, Bolivia, the West Indies, and Indonesia. Cocaine can be ingested, inhaled, insufflated, or injected. Cocaine increases excitatory amino acid concentrations in the brain by blocking the reuptake of biogenic amines such as serotonin, dopamine, norepinephrine, and epinephrine. Cocaine can affect multiple organ systems, mostly with its effects on the cardiovasculature system. Similar to other local anesthetics, cocaine blocks neuronal and cardiac sodium channels, which can lead to ventricular dysrhythmias and seizures. (170)(171)(172)(173)(174) Furthermore, cocaine blocks cardiac potassium channels, resulting in QT prolongation and potentially torsade de pointes. (173) Cocaine can predispose users to vascular occlusions by activating platelets and causes α-granule release, resulting in platelet aggregation. (175) Experiments in human volunteers demonstrate that smoking cocaine causes bronchospasm. (176)

As in the case of all poisoned patients, the initial emphasis must be on stabilization, based on the patient's symptoms, including fluid resuscitation, vasopressors, and respiratory support. If tracheal intubation is required, the use of succinylcholine is contraindicated because of potential rhabdomyolysis and hyperkalemia. In addition, plasma cholinesterase metabolizes both cocaine and succinylcholine and their simultaneous use could either prolong cocaine toxicity or lead to paralysis. (177) For severe cocaine toxicity, hyperthermia is the most critical vital sign abnormality and rapid cooling measures are paramount. A meta-analysis evaluating benzodiazepines and antipsychotics in animal models of cocaine toxicity found that both reduced mortality. However, benzodiazepine treatment reduced mortality by 52% compared with only 29% reduction in mortality with antipsychotics. (178) The use of a β-adrenergic antagonist is contraindicated because of the concern for the theoretical development of unopposed α-adrenergic stimulation. Any organ dysfunction caused by vasospasm not resolved with sedation, cooling, and volume resuscitation could be treated with vasodilators such as phentolamine. An acute coronary syndrome should be treated with standard measures. Although cocaine is rapidly metabolized, standard urine drug immunoassays readily detect the metabolite of cocaine, benzoylecgonine, which remains detectable in the urine for 2 to 3 days after the last use. (179) Long-term effects of chronic cocaine use include malnourishment, stroke, seizures, and movement and psychiatric disorders. (180)

OPIOIDS/OPIATES

The adolescent population is no exception when it comes to the opioid misuse and abuse epidemic. In 2016, almost 900,000 adolescents (3.6%) reported misusing opioids in the past year. (15) The number increases to over 2 million between ages 18 and 25 years. Opioids are alkaloids naturally derived directly from the opium poppy plant. These include

morphine, codeine, thebaine, and noscapine. Opioids are a broader class of substances capable of binding to opioid receptors. Semisynthetic opioids, such as heroin and oxycodone, are created by chemical modification of an opiate. A synthetic opioid is a chemical that is not derived from an opiate, and is capable of binding to an opioid receptor and producing opioid effects clinically. Depending on the opioid or opiate, onset of action and duration action can be quite variable.

Patients poisoned by opioids predictably display features of the opioid syndrome: mental status depression, hypoventilation, miosis, and hypoperistalsis. Opioid agonists cause hypoventilation by reducing the sensitivity of the medullary chemoreceptors to hypercapnia and depressing the ventilatory response to hypoxia. (181)(182) The combined loss of hypercarbic and hypoxic drive eliminates the stimulus to breathe; respiratory depression is the primary cause of death after overdose. Arteriolar and venous dilation secondary to opioid use may result in a mild reduction in blood pressure. True opioid-induced hypotension appears to be mediated by histamine release. Methadone may interfere with normal cardiac repolarization and produce QT interval prolongation with a predisposition to the development of torsade de pointes. (183)(184) Seizures should be anticipated in patients with meperidine, propoxyphene, tapentadol, or tramadol toxicity. Abrupt cessation after habitual use can induce withdrawal symptoms, which can include anxiety, irritability, diaphoresis, vomiting, and tremor. Although this withdrawal symptom has significant discomfort, as opposed to many sedative-hypnotics, it is not life-threatening.

Treatment of opioid/opiate toxicity is to ensure adequate hemodynamics and respiratory drive. Naloxone can be administered through various routes, including intravenous, intramuscular, intranasal, and subcutaneous. Standard intravenous dosing is 0.01 mg/kg, followed by 0.1 mg/kg if the response is not achieved. Naloxone infusion has been used when long-acting opioid/opiate has been ingested and respiratory depression events continue to occur. Patients should be monitored for a minimum of 3 to 4 hours after initial naloxone dosing for short-acting opioid/opiate (heroin) intoxication, though shorter times have occurred without significant complications. (185)(186) Longer observation times are warranted with longer-acting opioid analgesics. Alternative to naloxone administration is intubation and mechanical ventilation.

Standard urine immunoassays detect opiates by identifying a common metabolite to codeine, heroin, and morphine. Other semisynthetic and synthetic opioids are not routinely detected and will result in a negative opiate screening result. Confirmatory testing is recommended if a specific opioid/opiate needs to be identified.

Summary

- Substance abuse is common in adolescents, with almost 30% admitting to ever using alcohol and 25% ever trying an illicit drug.
- Most adolescents will abuse substances that are inexpensive and easily available including alcohol, nicotine products, over-the-counter medications, marijuana, and inhalants.
- Readily available urinary drug immunoassays may detect some categories of substance abuse. However, both false-positive and false-negative results commonly occur for many substances and may not clinically correlate with acute intoxication.
- It is important for primary care physicians to be knowledgeable about substances of abuse, and privately screen for use and abuse during age-appropriate physical examinations.
- Based primarily on expert consensus and clinical experience, symptomatic and supportive care is often sufficient for the clinical treatment of most intoxications. This includes hemodynamic support (intravenous fluids, vasopressors), airway management, and sedation for significant psychomotor agitation, psychosis, and delirium. However, more resources are necessary for the evaluation and treatment of associated substance use and behavioral health disorders and the secondary impact on caregivers and family.

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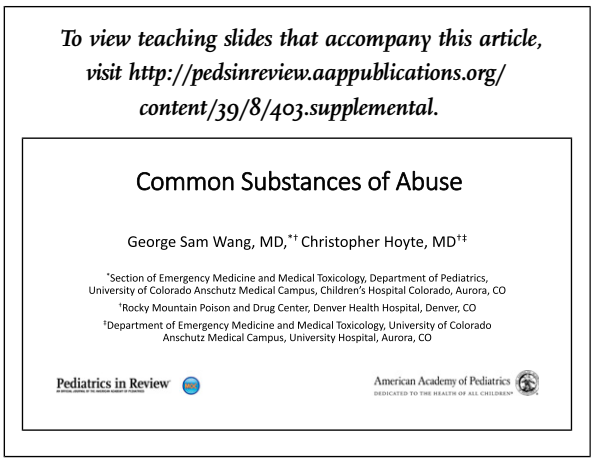

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1. A local district school health advisory council is implementing a drug education program for middle-school students. The program will focus on education by school nurses about the various substances of abuse and their dangers. While the program's discussion should cover all substances, based on reported abuse rates in junior high school, dangers surrounding the abuse of which of the following substances should be particularly emphasized by this program in this student population?
    A. Alcohol.
    B. Hallucinogens.
    C. Inhalants.
    D. Marijuana.
    E. Prescription medications.
2. An 11-year-old boy is brought to the clinic for his health supervision visit. He is healthy, has had no recent illnesses, and is not taking any medications. His parents report that he is a "good kid" who does well academically, but they worry about him being exposed to drugs and influenced by his peers at school. The clinician explains to the parents that their son is entering the age whereby part of the interview in the visit is done alone with the patient while the parents sit in the waiting room as the clinician conducts a psychosocial assessment. Based on the American Academy of Pediatrics recommendation, an annual tobacco, alcohol, and drug use assessment should be conducted beginning at the 11-year-old well visit. Which of the following is the preferred method for completing this screening for tobacco, alcohol, and drug use in this patient?
    A. Hair follicle analysis.
    B. High-performance liquid chromatography.
    C. Serum drug levels.
    D. Substance use, brief intervention, and/or referral to treatment guidelines.
    E. Urinary drug immunoassay.
3. A 16-year-old boy is brought into a school-based health clinic by his friends. He appears agitated and reports poor sleep over the past week. Vital signs show an increased heart rate, hypertension, and increased temperature. He is oriented to time, person, and place and exhibits no psychotic features. Abuse of which of the following substances is most likely responsible for this clinical presentation in this patient?
    A. Alcohol.
    B. Inhalants.
    C. Hallucinogens.
    D. Opioids.
    E. Stimulants.
4. A 17-year-old boy was brought to the emergency department by his roommate because of altered mental status. The roommate was away for the weekend and returned on Sunday night to find the patient lying on the couch, incoherent, and having unsteady gait. In the emergency department, the patient was noted to be sleepy with altered mental status, nystagmus, and ataxia. Which of the following substances of abuse is most likely responsible for the clinical presentation of this patient?
    A. Antihistamines.
    B. Ethanol.
    C. Inhalants.
    D. Sedative hypnotics.
    E. Stimulants.

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5. A 16-year-old female gymnast was sent from class to the school health room because she was "sleepy in class." The patient had back surgery for spondylolisthesis 6 weeks ago and restarted gymnastic training earlier this week. In the health room, she was noted to be sleepy, with shallow breathing and a low respiratory rate. 911 was called. The Emergency Medical Technicians (EMTs) assessed the patient to have depressed mental status, decreased respiratory rate, symmetric pinpoint pupils, and decreased bowel sounds. Pulse oximetry finding was 94% on room air. The patient was transported to the emergency department. The EMTs notified their supervising physician of the transport. Initial administration of which of the following en route is most likely to be recommended by the supervising physician?

   A. Benzodiazepines.
   B. Methadone.
   C. Naloxone.
   D. Oxygen.
   E. Sympathomimetics.