

# Novel Drugs of Abuse

George Sam Wang, MD,\*<sup>†</sup> Christopher Hoyte, MD<sup>†‡</sup>

\*Section of Emergency Medicine and Medical Toxicology, Department of Pediatrics, University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, Aurora, CO

<sup>†</sup>Rocky Mountain Poison and Drug Center, Denver Health Hospital, Denver, CO

<sup>‡</sup>Department of Emergency Medicine and Medical Toxicology, University of Colorado Anschutz Medical Campus, University Hospital, Aurora, CO

## Education Gaps

1. Although adolescent use of novel drugs of abuse is less common than traditional illicit drug use, it can be associated with significant morbidity and mortality.
2. Pediatricians and emergency medicine physicians should be knowledgeable about novel drugs of abuse to properly prevent and identify their abuse.

## Objectives After completing this article, readers should be able to:

1. Describe what is known about the epidemiology of novel drugs of abuse in adolescents.
2. Highlight the unique challenges associated with novel drugs of abuse.
3. Describe the pathophysiology, symptoms, and treatment for novel drugs of abuse.

## Abstract

Novel drugs of abuse are synthetic illicit drugs, or analogues of known illicit drugs, that can be more potent. Novel drugs of abuse are often labeled as *designer drugs*, *research chemicals*, *legal highs*, or *psychoactive substances*. They are often sold as designated legal or nondrug products, such as incense, plant food, or bath salts, with labeling such as "Not for Human Consumption" or "For Use in Research Only." The prevalence of use of novel drugs of abuse is difficult to determine because specific drugs, compounds, and availability of these drugs are constantly evolving. Changes in chemical structures lead to heterogeneity in physiologic response and clinical symptoms, even within the same category of drug. Pediatricians and emergency medicine physicians should be knowledgeable about novel drugs of abuse and their resulting symptoms for prevention and identification of their use.

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### ABBREVIATIONS

CNS	central nervous system
DEA US	Drug Enforcement Administration
GABA	$\gamma$ -aminobutyric acid
GHB	$\gamma$ -hydroxybutyrate
LSD	lysergic acid diethylamide
MTF	Monitoring the Future
PCP	phencyclidine
SC	synthetic cannabinoid

## NOVEL DRUGS OF ABUSE

In the most recent National Survey on Drug Use and Health, approximately 2.2 million, or 8.8%, of adolescents aged 12 to 17 years admitted to using any illicit drug, including marijuana, prescription medications, cocaine, hallucinogens, methamphetamines, inhalants, and heroin. (1) In 2017, the Monitoring the Future (MTF) survey reported that 9.4% of eighth-, 10th-, and 12th-graders admitted to using any illicit drug other than marijuana in the past year. (2) Novel drugs of abuse are newer synthetic illicit drugs, or analogues of known illicit drugs, that can be more potent and difficult to identify and detect. Prevalence of use is challenging because the specific drugs, compounds, and availability of these drugs are constantly changing. Despite the lack of accurate epidemiologic data, novel and synthetic drugs of abuse are a public health concern affecting adolescents. The use of novel drugs is associated with significant morbidity and mortality and can lead to significant medical consequences and outcomes from acute intoxication and associated polysubstance use. (3)(4)

Novel drugs of abuse are often labeled as *designer drugs*, *research chemicals*, *legal highs*, or *psychoactive substances*. Although the US Drug Enforcement Administration (DEA) has made distribution and use of many of these drugs illegal, there are several challenges that make monitoring and detection of these drugs difficult. (5) Drug manufacturers and distributors may sell them as designated legal or nondrug products, such as incense, plant food, or bath salts. They will also be sold with labeling such as “Not for Human Consumption” or “For Use in Research Only” to avoid any responsibility for their abuse and misuse. Drug manufacturers may develop the chemical to resemble other illicit drugs and slightly change the chemical structure, which makes them difficult to detect. Standard urine drug immunoassays do not detect these drugs, although detection may be performed in reference laboratories, if available. Changes in chemical structures lead to a heterogeneity in physiologic response and clinical symptoms from the same category of drug (Table). For example, synthetic cannabinoid (SC) intoxication can lead to mild symptoms such as sedation or more severe consequences such as seizures, hyperthermia, psychomotor agitation, and death. (6)

Many novel drugs of abuse are sold in convenience stores, publicly exchanged, and some are easily found on the Internet for purchase. The Dark Web, a part of the World Wide Web that is accessible only using specific coding or software, is also a potential source of distribution. (7) Contamination and quality control has been a long-standing problem with illicit drugs, and novel drugs of abuse are no

exception. Examples of contaminants in traditional illicit drugs of abuse are the addition of fentanyl in heroin or levamisole in cocaine. (8)(9)(10)(11)(12)(13)(14) Because there is no regulatory or oversight process in the drug manufacturing, the content or potency will also vary. Local public health emergencies and outbreaks have occurred from the distribution and use of novel drugs that are found to be significantly toxic or potent. (15)(16)(17)(18)(19)(20)

Because these drugs are difficult to detect, diagnosis is most often made by history, either by a witness or the patient, or by symptoms consistent with reported use of the drug. Most published research on novel drugs of abuse are case reports, media accounts of local outbreaks, and novel analytical techniques to help with detection. Drug manufacturers and recreational users will describe drug dosing and symptoms using Internet sources such as Erowid, Psychonautwiki, and Bluelight. (21)(22)(23)

## SYNTHETIC CANNABINOIDS

In 2010, more than 11,000 emergency department visits were associated with SCs, and 75% were in adolescents and young adults aged 12 to 29 years. (24) Fortunately, use among adolescents seems to have decreased. According to the MTF survey, past-year use of SCs in adolescents has declined since 2012, from 11.4% to 3.5%. (2)(25)(26) Despite this decrease, adolescents represent a large proportion of recreational users. In a multicenter prospective observational study of consultations performed by medical toxicologists, adolescents aged 13 to 18 years accounted for approximately 25% of patients presenting to health-care facilities for acute SC intoxication. (27) Comorbidities associated with SC use in adolescents include depressive symptoms and marijuana, alcohol, and polysubstance use. (3)(4)

Synthetic cannabinoids are chemically synthesized analogues of natural cannabinoids; they are not cannabis products. They are sold as the chemical itself in powdered form, or sprayed or applied to marijuana, dried herbs/plants, or other hallucinogenic plants. They are sometimes commonly referred to as *K2*, *Spice*, or *Buddha*. More than 200 known SCs have been identified. (28) Synthetic cannabinoids are agonists at the cannabinoid receptors in the central nervous system (CNS) that result in their psychoactive effects. They can have similar or increased potency on cannabinoid receptors compared with natural cannabinoids. Clinical symptoms are variable; common mild symptoms include ataxia, sedation, mydriasis, and tachycardia. More severe symptoms reported include psychomotor agitation,

psychosis, seizures, hallucinations, delirium, rhabdomyolysis, respiratory depression, and acute kidney injury. (29)(30)(31)(32)(33) Ischemic stroke, subarachnoid hemorrhage, myocardial ischemia and infarction, and death have also been reported. (34)(35)(36)(37) Treatment consists of sedation (including benzodiazepines, antipsychotics) to control psychomotor agitation and supportive care for associated end-organ toxicity. Standard urine drug immunoassays will not detect SCs and will not result in a positive tetrahydrocannabinol or respective metabolites. Confirmatory reference laboratory assays are available for some SCs, but they do not return in a timely manner to affect clinical care. However, as more SCs are developed, many are not detectable with available confirmatory assays.

## SEDATIVES

### Phenibut

Phenibut ( $\beta$ -phenyl- $\gamma$ -aminobutyric acid hydrochloride) was discovered and introduced in clinical practice in Russia in the 1960s for the treatment of anxiety, alcohol withdrawal, and insomnia. (38)(39) It is widely available for purchase on the Internet for recreational use. (40) Phenibut and its analogues have similar psychopharmacological action as baclofen and act primarily on  $\gamma$ -aminobutyric acid (GABA)-B receptors. It also stimulates GABA-A and dopamine receptors and antagonizes  $\beta$ -phenethylamine. The most reported route of phenibut use is by ingestion rather than by nasal insufflation or injection. (39)

Onset of symptoms is reported to occur 2 to 4 hours after oral ingestion and may last up to 24 hours. Symptoms from phenibut use include sedation, CNS depression, and ataxia. (38)(39)(40)(41)(42) Symptoms can be exacerbated when co-ingested with other sedatives/hypnotics. Other, more severe symptoms include hallucinations, agitation, and seizures. Treatment should be focused on ensuring adequate ventilation and providing sedation for psychomotor agitation. Similar to other GABA-A and GABA-B agonists, one should expect withdrawal to occur with abrupt cessation after chronic use with similar associated symptoms, including delirium, tremor, and seizures. (43)

### $\gamma$ -Hydroxybutyrate and Associated Compounds

According to the MTF, 0.7% of 12th-graders admit to past-year use of  $\gamma$ -hydroxybutyrate (GHB), (2) a federal schedule I drug. (44) Sodium oxybate, which is a GHB-containing pharmaceutical product, is a schedule III drug for cataplexy and narcolepsy. The endogenous GABA neurotransmitter is metabolized in small amounts to GHB naturally. 1,4-Butanediol and  $\gamma$ -butyrolactone are both metabolized

to GHB and can have similar clinical sequelae. These chemicals can be found in printing ink, cleaning agents, automotive products, and adhesives.

Most exogenous GHB is ingested, insufflated, or injected in powder or liquid form. They are GABA-B receptor agonists, which clinically lead to sedation, CNS depression, nausea, bradycardia, and respiratory depression. Classically, GHB will lead to rapid onset of symptoms, with peak concentrations within 30 to 40 minutes, followed by a rapid recovery a few hours later. (45) Respiratory support is the mainstay of treatment. Withdrawal symptoms have been described after chronic abuse. (46)(47) Reference laboratory analysis can be performed to detect GHB, 1,4-butanediol, or  $\gamma$ -butyrolactone.

### Kava

Kava is derived from the *Piper methysticum* plant. It can be referred to as *awa*, *kew*, or *tonga*. It can be smoked or prepared as a beverage or tea and is often used for relaxation or to treat anxiety. The active ingredients are kava lactones, which include methysticin, dihydromethysticin, kawain, and yangonin. (48) Although the exact mechanisms of action are unknown, kava lactones are thought to modulate the GABA neurotransmitter pathway, leading to the mild sedating clinical effects.

Acute use of kava is not expected to cause neuropsychiatric symptoms severe enough to require acute intervention or health-care evaluation. Several kava lactones have been shown to have CYP450 interactions (potent inhibitors), which could lead to drug interactions. (49) Long-term use has been associated with dermatitis, hepatotoxicity, nausea, and indigestion. (50)(51)

## HALLUCINOGENS/PSYCHOACTIVE DRUGS

### Phencyclidine and Analogues

Phencyclidine (PCP), ketamine, and their novel analogues are arylcyclohexamines that exhibit their dissociative effects by antagonizing *N*-methyl-D-aspartate receptors. (52) The Substance Abuse and Mental Health Services Administration reported that 2.5% of adolescents and young adults 12 years and older have used PCP in their lifetime. (1) Many novel PCP analogues have become available, including methoxetamine, 3- and 4-methoxyphencyclidine. (53)(54)(55)(56)(57) In contrast to PCP, ketamine is not well absorbed by the oral route, with limited bioavailability and significant first-pass metabolism. Also, PCP has a longer half-life and duration of action than ketamine. Ketamine has 10% of the affinity for the *N*-methyl-D-aspartate receptor than PCP, whereas

some other analogues, such as 3-methoxyphencyclidine, have higher affinity than PCP. (57)

Common symptoms include tachycardia, nystagmus, hypertension, euphoria, nausea, and vomiting. More serious effects include psychosis, delirium, hallucinations, and agitation. Users describe being in the “K-hole” when having their dissociated experiences. Life-threatening complications reported include coma, hypoventilation, apnea, and seizures. Treatment for PCP intoxication includes limiting external stimulation and giving sedation for psychomotor agitation, including benzodiazepines. Antipsychotics can be considered, but caution should be used because this may exacerbate hyperthermia, lower the seizure threshold, and have associated adverse effects, such as dystonic reactions. Phencyclidine is detected on some standard urinary drug immunoassays; false-positives can occur with exposures to dextromethorphan and diphenhydramine. Phencyclidine and ketamine analogues may not reliably cross-react with the PCP urine immunoassay.

### Lysergic Acid Diethylamide and Associated Analogues and Other Serotonergic Agonists

Lysergic acid diethylamide (LSD) has been abused for decades for its hallucinogenic properties. The MTF reports that less than 3% of all eighth-, 10th-, and 12th-graders admitted to using LSD in the previous 12 months. (2) There are several LSD analogues available, including N-allylnor-lysergic acid N,N diethylamide, and lysergic acid 2,4-dimethylazetidide. (58) Lysergic acid diethylamide and associated analogues are typically used in powder or blotter form via oral or sublingual administration and mediate their symptoms by activation of the serotonin 5HT-2A receptor. (59)(60) Analogues of LSD have similar onsets of action, but many of them have less reported euphoria and strength of effect compared with LSD. (59) 2-C drugs are hallucinogenic phenethylamines, which include 4-iodo-2,5-dimethoxyphenethylamine and 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl) phenethylamine. (61)(62)(63)(64) (65)(66)(67)(68) They have several slang terms, including *25i*, *2-C*, *2-I*, *2-CB*, *NBOMB*, and *N-BOMB*. They were initially developed for research purposes to study the 5HT-2A receptor because they are potent serotonin agonists. More analogues continue to be developed by substitutions to the base phenethylamine structure. Similar to LSD, 2-C drugs are often sold on blotter paper and used sublingually or orally.

Symptoms from both LSD analogues and 2-C compounds are variable but mostly consist of hallucinations, euphoria, tachycardia, and hypertension. Suicidality was described in a case report. (64) More significant adverse

effects include psychosis, agitation, seizures, hyperthermia, rhabdomyolysis, kidney injury, serotonin toxicity, and death. (65)(66)(67)(68) Laboratory abnormalities that may be found include elevated creatinine kinase, leukocytosis, hyperglycemia, and acidosis. Treatment is similar to that for other etiologies of agitated delirium and psychosis, including sedation with agents such as benzodiazepines and antipsychotics. (65) There has been a report of using cyproheptadine for serotonin toxicity resulting from a 2-C compound. (64) Routine testing for LSD analogues and 2-C compounds are not routinely available, and most exposures are determined by history and physical examination. Similar to other novel drugs of abuse, analytic detection methods may be limited due to the constant evolution of these compounds.

## OPIOID/OPIATE ANALOGUES

### Fentanyl, Analogues, and Synthetic Opioids

The MTF reported that trends in lifetime prevalence of narcotic use other than heroin in 12th-graders have declined from 13.4% in 2006 to 6.8% in 2017. (2) Fentanyl is a short-acting synthetic opioid agonist approximately 100 times more potent than morphine. The DEA has found a significant increase in fentanyl seized by law enforcement nationwide by almost 400% from 2013 to 2014. (69) The increase in use of fentanyl as a heroin substitute (intentionally or through adulteration) has been primarily responsible for an increase in US drug overdose deaths. Fentanyl is used via inhalation, intravenous access, or parenteral administration. Transdermal fentanyl in the form of a patch contains enough drug to create a transdermal gradient sufficient to achieve steady-state plasma concentrations for 3 days. After a fentanyl patch is considered exhausted, approximately 50% of the total dose remains. Fentanyl patch abuse can occur by application of 1 or more patches to the skin, by application of heat and an occlusive dressing, or by extraction of the drug from the patch reservoir. (70)

Many fentanyl analogues also exist that have been implicated in overdose deaths: carfentanyl (10,000 times more potent than morphine), sufentanil, and alfentanil. (71)(72) U-47700, sometimes referred to as *pink*, is another popular illegal synthetic opioid in which abuse has led to high mortality and morbidity. (71)(73)(74) Synthetic opioids have also been sold and mislabeled as diverted prescription opioid analgesics.

After overdose, patients present with the typical opioid toxidrome: CNS depression, miosis, and respiratory depression. Similar to the treatment of other opioid intoxication, the focus should be respiratory support by either mechanical ventilation or use of naloxone. Although fentanyl is more

TABLE. Novel Drugs of Abuse and Associated Clinical Symptoms

DRUG CATEGORY	CLINICAL SYMPTOMS		
	CARDIOVASCULAR	NERVOUS SYSTEM	OTHER
Synthetic cannabinoids	Tachycardia, hypertension, myocardial ischemia	Agitation, sedation, psychosis, seizures, delirium, ataxia	Hyperthermia, metabolic acidosis, acute kidney injury, rhabdomyolysis
Phenibut	Bradycardia, hypotension	Sedation, coma, ataxia, nystagmus	Respiratory depression
$\gamma$ -Hydroxybutyrate	Bradycardia, hypotension	Rapid-onset sedation and coma, ataxia, nystagmus	Respiratory depression
Phencyclidine and analogues	Tachycardia, hypertension, flushed	Agitation, delirium, sedation, mydriasis or miosis, ataxia, nystagmus, hyperreflexia, hallucinations	Hyperthermia, metabolic acidosis, acute kidney injury, rhabdomyolysis
Lysergic acid diethylamide and serotonergic agonists	Tachycardia, hypertension	Auditory and visual hallucinations, nystagmus, ataxia, psychosis, delirium, mydriasis, coma, hyperreflexia, clonus	Hyperthermia, metabolic acidosis, acute kidney injury, rhabdomyolysis
Fentanyl and synthetic opioids	Bradycardia, hypotension	Euphoria, sedation, coma	Respiratory depression
Cathinones	Tachycardia, hypertension	Agitation, psychosis, delirium, mydriasis, seizures	Hyperthermia, metabolic acidosis, acute kidney injury, rhabdomyolysis

potent than heroin, the dose of naloxone required to reverse respiratory depression seems to be similar to that of other common opioids. (75) The binding affinity of fentanyl at the  $\mu$  opioid receptor is similar to that of morphine and naloxone. (76)(77) However, if an exposure involves large quantities of fentanyl, or certain analogues, such as sufentanil, higher doses of naloxone may be required for reversal. (76) Fentanyl, fentanyl analogues, and other illicit synthetic opioids will not be detected on a standard urine drug immunoassay for opiates. Diagnosis should be made on history and clinical suspicion. Reference laboratories have detection methods for some of these novel opioid analogues.

### Loperamide

Loperamide is an insoluble meperidine analogue that is used to treat diarrhea. Although loperamide has been used for decades as an antidiarrheal, its use as a drug of abuse is novel. This medication is available without a prescription, and the paucity of adverse patient outcomes reported in the medical literature suggests that the safety profile of this agent is good. There is limited oral bioavailability of loperamide, thus large overdoses are required to achieve euphoria. There are several reports of use and abuse of loperamide for self-treatment of opioid addiction and to achieve euphoria similar to opioids. (78)(79)(80)(81)(82) Clinical signs of respiratory depression, miosis, and CNS depression may be present in large overdoses. The more concerning adverse

effect is cardiac dysrhythmia. Loperamide abuse may result in significant QT-interval prolongation and potentially life-threatening cardiac dysrhythmias. (83)(84)(85) Treatment consists of respiratory support and naloxone administration, if necessary. (86) Cardiac dysrhythmias should be treated accordingly for the specific cardiac abnormality. Detection of loperamide and its metabolites can be obtained from reference laboratories.

### Kratom

Kratom, or *Mitragyna speciosa*, is derived from a tree native to Asia and Africa and has been used to enhance productivity in manual laborers and to treat chronic pain and opioid withdrawal. (87) In the United States, kratom is primarily abused for euphoria and stimulant properties, as well as for pain, mood swings, and opioid-related withdrawal. (88)(89) There has been a 10-fold increase in regional poison center calls involving kratom: from 26 in 2010 to 263 in 2015. (90) Kratom produces both stimulant effects and opioid analgesic effects. The kratom alkaloids mitragynine and 7-hydroxymitragynine activate  $\mu$ -,  $\delta$ -, and  $\kappa$ -opioid receptors. Commonly reported symptoms include altered mental status, agitation, CNS depression, and tachycardia. (91) Hepatotoxicity and cholestasis have also been reported from kratom use. (92)(93)(94) There have been case reports of deaths associated with kratom use, but co-ingestants were also detected on postmortem examination. (95)(96)

Detection of mitragynine and its metabolites can be performed by reference laboratories.

## STIMULANTS

*Catha edulis*, commonly known as khat, is a plant that is commonly used as a stimulant in Africa and Middle Eastern countries such as Yemen. Leaves of the plant are often chewed, and the active ingredient, cathinone, is absorbed. As the leaves of the plant age, cathinone is degraded to cathine, which has about one-tenth the stimulant effect of D-amphetamine. (97)(98) The primary effects of khat are agitation, increased alertness, insomnia, euphoria, anxiety, and hyperactivity. Khat chewing is associated with cardiac and gastrointestinal complications. (97)(98)

Synthetic cathinones are popular novel drugs of abuse and are easily purchased through the Internet. The abuse of synthetic cathinones is widely reported via the media, which sometimes refers to these drugs as *zombie drugs*. (99)(100) Similar to SCs, synthetic cathinones are often sold as non-drug products such as bath salts or plant food. They are labeled as “Not for Human Consumption” to circumvent controlled substances legislation. Synthetic cathinones include methylone, mephedrone, butylone, methylenedioxypropylone, dimethylcathinone, ethcathinone, ethylone, and 3-and 4-fluoromethylcathinone. (99)(100) They have properties similar to amphetamines and have sympathomimetic effects, in addition to significant psychosis. (101) Similar to methoxydeoxymethamphetamine (ecstasy), some synthetic cathinones have been reported to cause hyponatremia, although the mechanism is unclear. (102)(103)(104)(105) Other reported complications include acute kidney injury and sudden cardiac death. (106)(107)(108)(109)(110) On September 7, 2011, the DEA used its emergency scheduling authority to make possession or sale of methylenedioxypropylone, methylone, and mephedrone illegal. (111) Symptomatic and supportive care is the mainstay for the treatment of cathinone toxicity. This includes sedation with benzodiazepines and antipsychotics and control of psychomotor agitation to prevent significant acidosis and end-organ toxicity. Cathinones are not identified on standard

urine drug immunoassays, and reference laboratory testing is needed if detection is indicated.

## Summary

- Novel drugs of abuse are also called *designer drugs*, *research chemicals*, *legal highs*, or *psychoactive substances*. They are often sold with labels warning “Not For Human Consumption.”
- Development of drug analogues by changing chemical structures leads to a heterogeneity in physiologic response and symptoms within the same category of drug. (5) This also makes laboratory detection difficult and limited.
- Based on observational studies, expert opinion, and case reports, diagnosis should be based on history and physical examination findings, and treatment should focus on symptomatic and supportive care.

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George Sam Wang, MD,<sup>†</sup> Christopher Hoyte, MD<sup>††</sup>

<sup>\*</sup>Section of Emergency Medicine and Medical Toxicology, Department of Pediatrics, University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, Aurora, CO

<sup>†</sup>Rocky Mountain Poison and Drug Center, Denver Health Hospital, Denver, CO

<sup>††</sup>Department of Emergency Medicine and Medical Toxicology, University of Colorado Anschutz Medical Campus, University Hospital, Aurora, CO

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1. A 16-year-old high school student is brought by emergency medical services to the emergency department on a Saturday at 9 pm with acute onset of ataxia, sedation, mydriasis, tachycardia, hallucinations, and agitation. The patient is accompanied by her 16-year-old friend who tells you that they were at a party where many "designer drugs" were being exchanged. You suspect marijuana or a similar drug. A urine toxicology screen is performed and is negative. Which of the following best explains the reason why the detection of designer drugs is so difficult?
  - A. Designer drugs are metabolized very quickly and are largely out of the system in minutes.
  - B. Polysubstance abuse causes interference in the assays.
  - C. Slight alterations in the chemical formula compared with the parent compound cause them to be undetectable in standard urine drug immunoassays.
  - D. The amount of drug in the system is too small for standard detection methods.
  - E. The ingestion of alcohol masks designer drugs.
2. On further questioning of the friend who accompanied the patient in question 1 to the emergency department, she states that the patient may have ingested "Spice" or "Buddha." In which of the following general categories of designer drugs does Spice belong?
  - A. Amphetamines.
  - B. Benzodiazepines.
  - C. Hallucinogenic drugs.
  - D. Opioid analogues.
  - E. Synthetic cannabinoids.
3. A 16-year-old boy presents to the emergency department with tachycardia, hypertension, nystagmus, psychosis, and agitation. You suspect phencyclidine overdose. Which of the following is the best initial treatment for this patient?
  - A. Antipsychotics.
  - B. Benzodiazepines.
  - C.  $\beta$ -Blockers.
  - D. Insulin and glucose.
  - E. Naloxone.
4. A 15-year-old boy is brought by emergency medical services to the emergency department with central nervous system depression, miosis, and respiratory depression. There are no friends or family members present to provide further information about the substance ingested. You turn to your medical student and mention that this is a classic toxidrome for a certain class of drugs. Overdose with which of the following substances is most likely to present with the classic toxidrome seen in this patient?
  - A. Amphetamines.
  - B. Benzodiazepines.
  - C. Cannabinoids.
  - D. Hallucinogens.
  - E. Narcotics.

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5. The parents of a 14-year-old who was brought to the emergency department with likely synthetic cathinone ingestion want to know how he could have gotten the drug since he is homeschooled and lives a solitary life on a family farm. Which of the following features of cathinone best explains this patient's easy access to these dangerous drugs?
- A. Commonly prescribed for patients with attention-deficit/hyperactivity disorder.
  - B. Derivatives of soybeans commonly found on family farms.
  - C. Easy to extract from simple bread mold.
  - D. Found in many common over-the-counter cold and flu preparations.
  - E. Sold legally as bath salts over the Internet.



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