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Drugs of Abuse 2012 Update

Recreational drug use and drug abuse are major health problems and they present a challenge to emergency physicians. The United States has 6% of the world population but accounts for 60% of the drug market. Since the mid-1990s, there has been a significant increase in the number of new drugs, and increased access to them, directly related to the Internet, which provides both drug information and information on how to obtain the drugs. This article comprehensively reviews the current management of drugs of abuse.

— Ann M. Dietrich, MD, Editor

Introduction

New drugs are constantly added to the market, many of them legal. Many new drugs with abuse potential are often called "legal highs," as they are not banned by the federal government or states. Also, products may be labeled "not for human consumption" to avoid the label of illegal. The European Monitoring Center for Drugs and Addiction Europol says 41 new drugs entered the market in 2010. The legal status of the more familiar recreational substances has encouraged users to seek newer options that offer the advantages of being legal, less expensive, less contaminated with adulterants, more readily available, or with more desirable pharmacological effects.

Since these drugs do not undergo clinical trials, the spectrum of their effects is unknown, the effects of overdose are unknown, and the emergency department (ED) management is uncertain.

The term "designer drugs" refers to chemicals created specifically for recreational use and to evade drug legislation, usually by modification of the molecular structures of existing drugs. Less commonly, drugs not structurally related to known drug classes are developed to mimic the desired effects of other drugs. Most drugs of abuse are members of one of the four distinct chemical families: the piperazines, phenethylamines, tryptamines, or piperidines (PCP is a member the piperidine class, but will not be discussed in this review). Recreational drugs can also be classified by their clinical effects as predominantly stimulant, ecstasy-like (entactogenic), sedative, or hallucinogenic. These features can, to a large extent, be predicted from the structure of each compound or chemical family. However, many designer drugs have a combined stimulant and psychoactive effect due to action at multiple CNS receptor sites.

The pharmacodynamic principles underlying our understanding of known drugs of abuse (e.g., amphetamines) help in predicting the effects and management of newer drugs based on their chemical structure. New drugs with predominately stimulant effects, such as BZP, mephedrone, and naphyrone, inhibit presynaptic reuptake of monoamines, particularly dopamine. Newer drugs with entactogenic action, such as phenylpiperazines or methylone, release serotonin from nerve endings, and newer hallucinogens such as 5-MeO-DiPT are serotonin receptor agonists. Other drugs, such as those found in salvia and mitragyna (kratom), affect opioid receptors.

Executive Summary

- The term "designer drugs" refers to chemicals created specifically for recreational use and to evade drug legislation, usually by modification of the molecular structures of existing drugs.
- Most phenethylamines have stimulant properties, although "designer" substitutions have created substances with additional or alternative psychoactive properties (MDMA).
- Serious complications of mephedrone ingestion have been reported in U.K. hospitals, including serotonin syndrome, delirium due to mephedrone-induced hyponatremia, as well as acute myocarditis.
- Bromo-Dragonfly, B-Fly, or the "FLY" is a new hallucinogen recently on the market. It has both stimulant and hallucinogenic effects.

As mentioned, evidence from randomized controlled trials or even observational studies is often not available, leaving the clinician to base management decisions on clinical presentation, consensus statements, and case reports. In addition, there are numerous websites that provide information regarding effects and side effects (e.g., Erowid) and may provide additional information. The information available online must be viewed with caution; most of these drugs have not been studied with animal or human trials.

In addition to the acute presentation, the practitioner must also be aware of the complications of long-term use. A national survey recently reported that 1.8% of chronic drug users have at least one ED visit. If there is an associated drug use disorder, this number rises to 3.7%.[1] Heroin and inhalant use had the highest rates of ED visits, and marijuana had the lowest. Persons with social supports (e.g., marriage) had lower rates, and those with psychopathology had higher rates.

Stimulants

The phenethylamines are a large family of monoamine alkaloids that includes the familiar drugs of abuse amphetamine and methamphetamine. Amphetamines are psychoactive substances with stimulant, euphoric, anorectic, and, in some cases, empathogenic, entactogenic, and hallucinogenic properties. Most phenethylamines have stimulant properties, although "designer" substitutions have created substances with additional or alternative psychoactive properties (MDMA). Iodine and bromine substituted phenethylamines are relatively more hallucinogenic than the hydrogen and nitrogen equivalents (Bromo-Dragonfly).

Amphetamine. Drugs that cause CNS stimulation occur in many plants such as *Ephedra sinica* and have been used for centuries. *E. sinica* has been used in Chinese herbal medicine for 5,000 years as ma huang, which is still readily available in Chinese herbal stores and on the Internet. It is used for respiratory problems (asthma), weight loss, and to increase energy. Ephedrine is a common ingredient of medicines used for treatment of the common cold and was available over the counter in the United States until recently.

The search for a synthetic ephedrine substitute led to the development of amphetamine-type stimulants. Amphetamine ("speed") was first synthesized in 1887. Methamphetamine was first developed in Japan in 1919 and used as a bronchodilator and nasal decongestant. It has been used since 1932 as a treatment for asthma for its bronchodilating properties. They were also used for the treatment of narcolepsy, hyperactivity in children, weight loss, and to maintain an awakened state for truck drivers. In 1967, prescriptions for amphetamine reached a peak, with 31 million prescriptions and 10 billion tablets manufactured in 1970.[2] Increased availability led to abuse, and the negative consequences became more prevalent. In 1970, amphetamines were classified as a Schedule II drug.

Methamphetamine ("Ice," "Crystal Meth"). Methamphetamine was developed as an amphetamine derivative and quickly became a popular medication during the 1940s and 1950s, being prescribed for a variety of indications. During the 1960s, an increasing awareness of the adverse health effects associated with methamphetamine led to the withdrawal of most of the indications for licit methamphetamine use and declines in legal production of the drug. However, the illicit manufacture of methamphetamine increased to meet the demand, and methamphetamine use has become a major health problem. Abuse has increased with variable geographic penetrance over the last 30 years.[3] In 2005, the estimated production was 290 tons, with a dose range of 5 to 150 mg per dose (United Nations Office on Drugs and Crime). Like amphetamines, its popularity is due to its ability to cause euphoria and increase energy and alertness.

Methamphetamine is a potent stimulant, inexpensive, and easy to make, with an estimated worldwide use by 35 million people. It may be taken orally, intravenously, or inhaled. Methamphetamine use led to 94,000 ED visits in 2005.[4]

Dextroamphetamine. Dextroamphetamine is a psychostimulant drug that is known to produce increased wakefulness and focus as well as decreased fatigue and decreased appetite. This chemical is legally prescribed but is also a drug of potential abuse because of

its stimulant effects. It is used for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. The dextroamphetamine salts constitute about 75% of the ADHD drug Adderall. Dextroamphetamine is also an active metabolite of the prodrug lisdexamphetamine (Vyvanse), as well as of several older N-substituted amphetamine prodrugs used as anorectics, such as clobenzorex (Asenlix), benzphetamine (Didrex), and amphetaminil (Aponeuron). Clinically, it acts like amphetamines and adverse effects and ED management are the same.

Mechanism of Action. Methamphetamine is a synthetic amine that acts as a potent stimulator by increasing sympathomimetic hormone concentrations in both the central and peripheral nervous systems. Methamphetamine is an indirect sympathomimetic agent that is distinguished from amphetamine by a more rapid distribution into the CNS, with a rapid onset of desired euphoria.[3] It is an indirect agonist of dopamine, noradrenaline, and serotonin receptors. Methamphetamine produces these effects by affecting the release and uptake of serotonin and catecholamine.

Clinical Effects. Amphetamines increase attention and decrease fatigue, increase activity, and decrease appetite. In addition, they have the psychological effects of euphoria and a rush sensation. Methamphetamine causes a range of direct effects, including euphoria, arousal, and psychomotor stimulation. Higher doses can cause an acute psychotic reaction. The side effects of chronic use are significant and also lead to ED visits.[6] Clinicians should consider the diagnosis of methamphetamine intoxication in any diaphoretic patient with hypertension, tachycardia, severe agitation, and psychosis.

Adverse Reactions. Multiple serious or life-threatening effects are possible with amphetamine intoxication. Seizures are possible, although usually brief. Hypertension and hyperthermia can also occur. Severe agitation may occur on presentation or at any time during the ED course. Violent behavior should be expected at any time. In addition to the danger to patient and staff, this behavior can cause or worsen hyperthermia, hyperkalemia, and rhabdomyolysis. Pulmonary problems with amphetamine use include acute noncardiogenic pulmonary edema, pulmonary hypertension, and dyspnea. CNS complications include hyperreflexia, seizures, cerebrovascular accident from hemorrhage or vasospasm, cerebral edema, and cerebral vasculitis. Cardiovascular problems include chest pain, dysrhythmias, palpitations, and hypertension. High catecholamine levels are known to be cardiotoxic, causing vasoconstriction, vasospasm, tachycardia, and hypertension.[7] The cardiovascular life-threatening consequences of methamphetamine use include acute coronary syndrome, myocardial infarction, aortic dissection, and sudden cardiac death, possibly due to fatal dysrhythmias. In addition, patients with acute methamphetamine intoxication may, without provocation, abruptly develop severe agitation and manifest extreme violence.

ED Management. Initial stabilization is based on clinical presentation and vital signs. When the patient is stabilized, the following tests are performed: finger-stick glucose (evaluation of altered mental status); serum electrolytes; serum lactate; creatinine phosphokinase (CPK); liver function studies (ALT, AST); arterial blood gas; PT, PTT; renal function studies (creatinine, BUN); acetaminophen and salicylate levels (possible co-ingestion); ECG (possible additional drug ingestion that causes prolonged QRS or QTc intervals); and pregnancy test.

The toxicological screen will pick up amphetamines, but both false positives and false negatives can occur. A false positive will occur if the patient is taking benzphetamine, bupropion, or selegiline. False negatives can occur if the screen is too early or late due to timing of the test after ingestion.

Management of Complications.

Airway Management. When indicated, patients may require intubation. Succinylcholine is contraindicated because of potential for hyperkalemia.

Seizures. These usually are brief, but if prolonged, use lorazepam or diazepam and seek other causes (hypoglycemia, intracranial hemorrhage).

Hyperthermia. Aggressive sedation, neuromuscular paralysis, and fluid resuscitation are used to control methamphetamine-induced hyperthermia; these measures can be supplemented with external cooling blankets or evaporative cooling techniques.

Hypertension. Hypertension is managed as other hypertensive crisis, and interventions are based on the severity of the hypertension.

Rhabdomyolysis. Rhabdomyolysis can cause acute renal failure and hyperkalemia. While the need for early, aggressive volume expansion is universally accepted, the fluid composition is more controversial, especially regarding the concept of urine alkalization. The administration of both normal saline and sodium bicarbonate is appropriate, especially in patients with metabolic acidosis.

Electrolyte Abnormalities. Severe hyperkalemia, particularly when associated with electrocardiogram changes, requires immediate administration of calcium to prevent arrhythmias, followed by temporizing measures to shift potassium intracellularly.

Agitation. Administer intravenous benzodiazepines (lorazepam 4 mg or diazepam 5 to 10 mg IV) to control agitation. These doses may need to be repeated at frequent intervals based on clinical response. Sometimes large cumulative doses may be required.

Second-generation antipsychotic agents (e.g., ziprasidone 10 mg IM), butyrophenones (e.g., droperidol 2.5 to 5 mg, or haloperidol 10 mg given IM or IV), or combinations of these agents can be used as adjunctive therapy when benzodiazepines do not adequately control symptoms.

Ecstasy (MDMA)

Ecstasy. MDMA, or ecstasy, was developed in the 1920s as an

Table 1. Serotonin Syndrome (Hunter Criteria)

Patient has taken a serotonergic agent and has one of the following:

- Spontaneous clonus
- Inducible clonus and agitation or diaphoresis
- Ocular clonus and agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia
- Temperature above 38°C and ocular clonus or inducible clonus

appetite suppressant. It was used by psychotherapists in the 1980s to promote enhanced social intimacy, increased empathy, and emotional openness. MDMA use increased in the 1990s,[8] followed by a decrease in usage from 2001-2005. Since then, adolescents' MDMA use has increased.

Mechanism of Action. MDMA is a substituted amphetamine with both dopamine- and serotonin-releasing and re-uptake inhibition properties. Amphetamines with methylenedioxy substitutions on the phenyl ring (MDMA) have both hallucinogenic and stimulant actions at relatively low doses and may represent a novel class of hallucinogens.[5] Metabolism occurs within the liver through the P450 system.

Clinical Effects. The desired effects of euphoria, increased energy, and sexual arousal begin within 30 minutes of ingestion and last for 4–6 hours.

Adverse Effects. Negative psychological effects include confusion, defensiveness, mental fatigue, anxiety, depression, panic disorder, and paranoia. Negative physical effects include the hyperpyrexic syndrome: severe hyperpyrexia, muscle rigidity, altered mentation, rhabdomyolysis, acute renal failure, lactic acidosis, hepatotoxicity, DIC, and multi-organ failure. In addition, milder temperature elevation, cardiac arrhythmias, and hypertension may be present; hyponatremia has been reported. These effects are thought to be serotonin related, causing a serotonin syndrome (*see Table 1*) due to the blocking of the re-uptake of serotonin. In numerous case reports, MDMA was associated with rhabdomyolysis, hyperkalemia, shock, acidosis, hypo- and hypercalcemia, hyponatremia, hypoglycemia, coagulopathy, seizures, acute kidney injury, hepatotoxicity, pancreatic necrosis, cerebral edema, cardiac and cerebral ischemia, acute respiratory distress syndrome, pulmonary edema and injury, gluteal compartment syndrome, multifocal hemorrhages, cardiac conduction abnormalities and arrhythmias, persistent neurologic deficits, and death.[9] Overdose can be fatal and the drug has been used for suicide attempts.[10]

Fatal hyperthermia may be due to a higher dose ingested, physical activity, and concurrent use of other stimulants or individual response.[10] Although there are no controlled studies, hyperthermia may be an indicator of a more serious course.

ED Management. As with most designer drugs, there is a lack of evidence-based medical investigations, and most treatments are supportive and symptom-determined. There has not been a controlled study, so most of the information is from case reports and online reports. An article published in 2010 summarized all the available information in the literature to date.[9]

The initial management is similar to that for amphetamines (see amphetamines section above).

Hyperthermia. Rapid cooling, as for heat stroke, is imperative. Dantrolene has been recommended for the treatment of hyperpyrexia associated with MDMA use.[11] It is conjectured that the apparent benefit of using dantrolene to treat MDMA-induced hyperpyrexia is secondary to a reduction in heat generation in skeletal muscle without treatment of the centrally mediated cause. This rationale has been questioned by toxicologists who believe that hyperpyrexia caused by MDMA is centrally mediated via serotonin, whereas dantrolene acts peripherally at skeletal muscle. The dosing of dantrolene varies considerably in different reports; however, the most common dose used was 1 mg/kg (max 80 mg) and continuing until symptoms subside or the maximum cumulative dose of 10 mg/kg has been reached.

Hyponatremia: Hyponatremia is reported commonly with MDMA use. It may be an effect of the drug directly or secondary to water intoxication due to associated increased thirst and physical activity. Asymptomatic mild hyponatremia without evidence of dehydration can be treated with fluid restriction alone. Asymptomatic and mild hyponatremia will usually resolve within 12 to 24 hours.

MDMA use can result in severe hyponatremia that can lead to neurologic symptoms such as confusion, seizures, cerebral edema, brain herniation, and death. Hyponatremia due to ecstasy use may have fewer complications of treatment than other causes of acute hyponatremia because of its rapid development and less time for fluid shifts within the brain. Regardless, correction should be achieved with caution. Overly rapid correction of hyponatremia can cause the demyelination syndrome (also called central pontine myelinolysis).

Patients with marked hyponatremia with neurologic symptoms may be treated initially with hypertonic saline to reduce neurologic symptoms. Once severe symptoms are controlled, further correction of hyponatremia must proceed with caution.

Ecstasy Impersonators

Paramethoxyamphetamine (PMA) ("red mitsubishi," "killer"), paramethoxymethamphetamine

(PMMA), and 4-methylthioamphetamine (MTA) ("flatliner") are often marketed as ecstasy but have different chemical structures. P-methoxyamphetamine (PMA) is not a new recreational drug. Paramethoxyamphetamine and MDMA both appeared in recreational use during the 1970s and both were sold as ecstasy. It is a methoxylated phenethylamine derivative, being one of a group of drugs also known as ring-substituted amphetamines or amphetamine derivatives.

PMA is structurally most similar to mescaline, which corresponds to its comparatively greater hallucinogenic properties.[12]

Its derivative is PMMA. PMMA appeared later on the illegal drug scene than PMA, in the 1990s and 1970s, respectively. Since then, numerous reports about fatalities have been in the literature.[13,14] Paramethoxymethamphetamine (PMMA) and 4-methyltrioamfetamine (4-MTA) have resulted in apparently greater morbidity and mortality rates than for other phenethylamines. PMA has a street name of "killer" and PMMA "death" and MTA "flatliner."

Fatal cardiac arrhythmia or fatal epileptic insults may occur. The mechanism could perhaps be compared with epilepsy-related cardiac shock due to activation of the autonomic nervous system

Clinical Effects. PMMA is used for intense stimulation and alertness, euphoria, empathy/feelings of closeness, sociability, and talkativeness. It is also used to intensify sensory experiences and enhance sexual arousal. Hallucinations are reported at higher doses.

Adverse Effects. Clinical adverse effects include hyperthermia, probably resulting from severe serotonin toxicity arising from the combined effects of marked serotonin release and strong monoamine oxidase inhibition. The clinical features of PMA poisoning are similar to those of MDMA and other ring-substituted amphetamines, including tachycardia, hypertension, hyperthermia, nystagmus, muscle spasm, bruxism, visual hallucinations, and, in severe cases, cardiac arrhythmias, respiratory failure, renal failure, seizures, and death. A frequent presentation includes severe hyperthermia (greater than 42° C) (*see Table 2*), and ingestion of these chemicals should be in the differential of patients with unexplained hyperthermia. Most fatal cases published in the literature had hyperthermia with a core temperature ranging between 39° C and 42.8° C.

ED Management. Benzodiazepines have been used for agitation and seizures. For hyperthermia, rapid cooling and dantrolene can be used. Hyponatremia can be treated with hypertonic saline or water restriction (see management for amphetamines and ecstasy).

Cathinones

Cathinone is a naturally occurring beta-ketone amphetamine analog found in the khat plant *Catha edulis* in East Africa and the Arabian peninsula. The leaves are chewed for its stimulant effects. Since its efficacy diminishes rapidly after the leaves are picked, it was previously not widely available outside of its endemic area. Overnight delivery has made it available worldwide. The chemicals in the khat plant have low toxicity, but use has been associated with AMI in susceptible patients.[15] Cathinone is chemically similar to ephedrine, cathine (d-norpseudoephedrine), and other amphetamines. The drug's maximum effect occurs after 15–30 minutes. Metabolism of cathinone is rapid, and only a small fraction of the molecule appears unchanged in the urine. Most cathinone is metabolized to norephedrine and is excreted in this form. Because cathinone is purported to bind to the dopamine transporter, this may explain why it is used for its cocaine- and amphetamine-like effects.

Synthetic cathinones include butylone, dimethylcathinone, ethcathinone, ethylone, 3 and 4 fluoromethcathinone, mephedrone, methedrone, and methylone. They have shown a dramatic increase in use since 2007, in part from sensationalized media attention and easy availability on the Internet.[16] These drugs can be used nasally or ingested and may be administered by the rectal, gingival, intramuscular, or intravenous routes. One derivative, bupropion (Wellbutrin), is used to treat depression and nicotine addiction.

Mephedrone. One of the more popular synthetic cathinones is mephedrone or 4 methylmethcathinone. It goes by a variety of names, including "bath salts," "vanilla sky," "ivory wave," and "meow-meow."

Drugs referred to as "bath salts" have only been in the general press for a few years. The *Morbidity and Mortality Weekly Report* published a report on May 20, 2011, of a study done with the Michigan Children's Hospital and Michigan Poison Control Center.[17] In that report, there was one death, and most of the 35 patients seen in EDs had coexistent psychiatric problems (bipolar, depression, schizophrenia) and many had other psychotropic medicines on drug screens. Overdose is a risk because the amount needed for effect may be as little as 5 mg of the drug, but packages may contain as much as 500 mg.[10]

Mephedrone is often cited as the fourth most commonly used drug (after cannabis, ecstasy, and cocaine) and the most commonly used "legal high."[13] Mephedrone, as of July 2012, is Schedule I, meaning it is illegal to manufacture, buy, possess, or distribute without a DEA license.

Methylone, Ethcathinone. Methylone is often marketed as high purity plant food. It was developed in 1996 for Parkinson's disease and depression. Ethcathinone poisoning has been associated with seizures and hyponatremia.[18] Clinical effects, adverse effects, and ED management are the same as for mephedrone.

Mechanism of Action. Epidemiological data and the effects of mephedrone and other cathinones are limited to unconfirmed user reports and clinical case series. There are no published preclinical studies or human clinical pharmacology studies of mephedrone, and there

Table 2. Complications of Hyperpyrexia Syndrome[11]

- Delirium and agitation
- Seizures
- Rhabdomyolysis
- Hyperkalemia
- Arrhythmias
- Metabolic acidosis
- Myocardial ischemia
- Cerebral ischemia
- Cerebral edema
- Acute kidney injury
- Pulmonary edema
- Acute respiratory distress syndrome
- Hepatotoxicity
- Coagulopathy
- Shock necessitating vasotropic/inotropic support

Adapted from: Grunau BE, Wiens MO, Brubacher JR. Dantrolene in the treatment of MDMA-related hyperpyrexia: A systematic review. *CJEM* 2010;12:435-442.

are no pharmacological guidelines for acute and chronic intoxication. Probably because of structural similarity, mephedrone shares psychoactive properties of cocaine, amphetamines, and MDMA. It most likely stimulates the release of, and then inhibits, the re-uptake of monoamine neurotransmitters.

Clinical Effects. Mephedrone is a water-soluble, white or colored (yellowish, beige, or brown) powder. It may be taken orally, nasally, or injected. It is usually sold as a white crystalline or an off-white yellow powder (the hydrochloride salt). The desired effects of mephedrone include euphoria, increased energy, feelings of empathy, and increased libido. It presents similar to a sympathomimetic or serotonin syndrome. (*See Table 1.*) Mydriasis, anxiety, agitation, paranoia, bruxism, aggression, depression, hallucinations, delusions, and manic behavior and seizures have also been reported from mephedrone use.

Adverse Effects. Serious complications of mephedrone ingestion have been reported in U.K. hospitals, including serotonin syndrome, delirium due to mephedrone-induced hyponatremia, as well as acute myocarditis. Forensic examiners in the Netherlands recently attributed the death of a 36-year-old man to mephedrone ingestion, following a period of excited, agitated delirium.[11,14] There are reports of seizures, psychosis, self-harm, severe toxic delirium, myocarditis, homicide, and acute kidney injury (AKI) related to mephedrone use.[15,16,19] Injected "bath salts" have caused necrotizing fasciitis.[20] AKI may be due to acute renal tubular necrosis, rhabdomyolysis. These substances may promote severe renal arteriolar vasospasm in a manner similar to cocaine, thereby producing renal hypoperfusion and renal ischemia, resulting in acute tubular necrosis. In addition, they may be directly toxic to tubular cells, inducing nephrotoxic acute tubular necrosis.

ED Management. Limited data exist regarding the most effective treatments for mephedrone ingestion. However, as in the management of other drugs causing sympathomimetic toxidromes, a case series published in the United Kingdom supports the use of benzodiazepines for treating the agitation associated with the acute toxidrome.[21] Based on these previously published reports in Europe, poison control protocols, and concerns for exacerbation of hyperthermia, rigidity, or seizures with antipsychotic use, a mixture of benzodiazepines, intravenous fluids, and other supportive measures is appropriate management.

Pyrovalerone and Related Drugs. Pyrovalerone (Centroton, Thymergix, O-2371) is a psychoactive drug with stimulant effects acting as a norepinephrine-dopamine reuptake inhibitor (NDRI), and is used for the clinical treatment of chronic fatigue or lethargy and as an anorectic or appetite suppressant for weight loss purposes. Although pyrovalerone is still occasionally prescribed, it is used infrequently due to problems with abuse and dependence. Pyrovalerone is a Schedule V controlled substance in the United States and is the only stimulant in that category. It is structurally related to a number of other stimulants, such as MDPV and prolintane (Promotil, Katovit). Side effects of pyrovalerone include anxiety, fragmented sleep or insomnia, and trembling, shaking, or muscle tremors. Withdrawal following abuse upon discontinuation often results in depression.

Naphyrone. Only months after the statutory instrument controlling mephedrone, the press was already reporting on the "new killer drug," naphyrone. Naphyrone has a chemical structure close to pyrovalerone and is a potent stimulant. It is 10 times stronger than cocaine.[22]

Drugs such as d-amphetamine, which interact selectively with the DA transporter, have psychostimulant properties; those such as MDMA that interact selectively with the 5-HT transporter have "empathogenic" profiles, whereas triple uptake inhibitors, such as cocaine and naphyrone, combine these properties.[23,24] The high potency of naphyrone compared to other cathinones suggests that it is likely to be associated with a higher risk of accidental overdose.

MDPV (methylenedioxypyrovalerone). Methylenedioxypyrovalerone (MDVP) was first detected in June 2007 in Germany. This drug is a variant of pyrovalerone and acts by releasing and inhibiting the reuptake of the monoamine neurotransmitters. It is reported to have amphetamine-like stimulant effects.[25]

Methylenedioxypyrovalerone (MDPV) and 3,4-methylenedioxy-α-pyrrolidinopropiophenone (MDPPP) have no entactogenic action but are purely stimulant according to collated Internet user accounts; this is perhaps surprising given their chemical structure. Reports suggest a duration of action of about 48 hours. Clinical features are of typical stimulant toxidromes,

including vasoconstriction and agitation or panic attacks. It is the most common chemical found in "bath salts" in the United States.

Mechanism of Action. As a triple reuptake inhibitor, naphyrone has been shown in vitro to affect the reuptake of the neurotransmitters serotonin, dopamine, and norepinephrine by interacting with the serotonin transporter, dopamine transporter, and norepinephrine transporter.

MDPV is a member of a family of more than 30 chemicals that exhibit activity as reuptake inhibitors of dopamine and norepinephrine, some of which may have nine times the potency of cocaine at the DAT. Metabolism of MDPPP is by demethylenation.[12]

Clinical Effects. The desired effects are feelings of euphoria and increased alertness, sociability, and empathy. Oral, intranasal, intramuscular, intravenous, and rectal routes of administration are reported. Oral (swallowing powder, capsules, or tablets) and intranasal routes are predominant. Clinical effects usually occur 15–45 minutes after oral ingestion and last approximately 2–5 hours. Effects usually occur 30 minutes after intranasal administration and last approximately 2–3 hours. The high lasts approximately 10–15 minutes after intravenous injection, with an overall duration of 30 minutes.[26] Mixed routes (oral and intranasal, oral and rectal) have been reported during a single session.

Adverse Reactions. Only a few reports are available in the medical literature, so much of what is known about naphyrone is from case studies and information on the Internet. Patients who have taken naphyrone have developed hyperthermia, hypertension, agitation, seizures, and renal problems.

Reports in the medical literature have linked MDPV use with hyperthermia, tachypnea, tachycardia, and cardiac arrest. Two cases of paranoid psychosis in individuals consuming MDPV have been reported.[27]

ED Management. There is no specific antidote to naphyrone, so management is based on clinical presentation.

Piperazines: BZP (n-benzylpiperazine). Piperazines were developed as anti-helminthic agents in the 1950s, and benzylpiperazine or BZP was evaluated as an antidepressant in the 1970s. This development was terminated once amphetamine-like effects were noted. There are, however, non-stimulant piperazine compounds with legitimate medicinal uses, such as cyclizine (1-diphenylmethyl-4-methylpiperazine) and precursors of trazodone.

Recreational use of piperazines was first reported in California in the 1990s and, subsequently, these agents have become widely used. Only in more recent times have they become subject to widespread control measures. Piperazines are often constituents of tablets sold as "ecstasy," often with more than one piperazine type in each tablet.[12] The piperazines are not closely chemically related to any of the more familiar recreational drugs. Although sometimes marketed as "herbal" or "natural" preparations, members of this family of drugs are fully synthetic in the sense that, unlike tryptamines or phenethylamines, there are no examples found in nature. A recent study has shown that mixtures of BZP with other piperazine drugs such as TFMPP (3-Trifluoromethylphenylpiperazine) share certain pharmacodynamic traits with MDMA.

Mechanism of Action. BZP has amphetamine-like actions on the serotonin reuptake transporter, which increase serotonin concentrations in the extracellular fluids surrounding the cell, thereby increasing activation of the surrounding serotonin receptors. BZP has a lower potency effect on the noradrenaline reuptake transporter and the dopamine reuptake transporter. BZP has a high affinity action at the alpha2-adrenoreceptor, it is an antagonist at the receptor, like yohimbine, which inhibits negative feedback, causing an increase in released noradrenaline.

BZP also acts as a non-selective serotonin receptor agonist on a wide variety of serotonin receptors; binding to 5HT2A receptors may explain its mild hallucinogenic effects at high doses, while partial agonist or antagonist effects at the 5HT2B receptors may explain some of BZP's peripheral side effects, as this receptor is expressed very densely in the gut, and binding to 5HT3 receptors may explain the common side effect of headaches, as this receptor is known to be involved in the development of migraine headaches.

Clinical Effects. The effects of BZP are largely similar to amphetamines, with one study finding that former amphetamine addicts were unable to distinguish between dextroamphetamine and BZP administered intravenously. Users report alertness, euphoria, and a general feeling of well-being. Sensations such as taste and visual and auditory perceptions are enhanced. The average duration is longer than that of dextroamphetamine, typically lasting 4–6 hours, with reports as long as 8 hours depending on the dose.

Adverse Reactions. Major side effects include dilated pupils, blurred vision, dryness of the mouth, extreme alertness, pruritus, confusion, agitation, tremor, extrapyramidal symptoms (dystonia, akathisia), headache, dizziness, anxiety, insomnia, vomiting, chest pain, hallucinations, paresthesia, tachycardia, hypertension, palpitations, collapse, hyperventilation, sweating, hyperthermia, and problems with urine retention. The more severe toxic effects include psychosis, renal toxicity, respiratory failure, hyperthermia, serotonin syndrome, rhabdomyolysis, and seizure.

ED Management. Management is based on clinical presentation. Treatment is similar to management of amphetamine overdose.

Gamma-hydroxybutyrate (GHB). Gamma-hydroxybutyrate (GHB) is an endogenous inhibitory neurotransmitter. It is synthesized from gabba-aminobutyric acid (GABA) in cells containing glutamic acid decarboxylase, the marker of GABAergic neurons. GHB is accumulated by the vesicular inhibitory

amino acid transporter and released by depolarization via a calcium-dependent mechanism. In the 1980s GHB was marketed as a drug that would promote muscle growth, aid sleep, and increase sexual performance. It was popularized when it was labeled as the "date rape drug." GHB and its chemical analogues have many street names. The most commonly used are "G" or "liquid ecstasy." The comparison to ecstasy is due to the euphoric, disinhibiting, and social effects, but the two substances are pharmacologically different.[28] GHB may be found as the sodium salt, which is a white crystalline powder dissolved in water to form an odorless and colorless solution. Most of the time, it is taken by mouth. The intranasal or intravenous routes are less frequently used. A low dose (0.5 g) is taken for relaxation and disinhibition, and a larger dose (1 g) for euphoric effect and some stimulant-like effects; a 2- or 3-g dose can induce deep sleep. Ethanol increases the soporific effects. The latter is why the drug can be used as a "date rape drug."

Mechanism of Action. GHB binds to GABA-B and GHB-specific receptors, which leads to an increase in dopamine and other neurotransmitters in the brain. GHB is a central nervous system (CNS) depressant, but its specific action has not yet been elucidated. In humans, GHB has been shown to inhibit the elimination rate of ethanol. This may explain the respiratory arrest that has been reported after ingestion of both drugs.

Clinical Effects. Clinical effects of GHB are comparable with those of alcohol or benzodiazepines. These effects usually occur 15 minutes after ingestion and can last approximately 3–4 hours.

Adverse Reactions. Respiratory depression or arrest is the most serious complication of GHB use.

ED Management. Management is supportive. Secure the airway as needed. The possibility of sexual assault should be considered.

Marijuana and "Spice" or "K2." Marijuana has been used as an agent for achieving euphoria since ancient times; it was described in a Chinese medical compendium traditionally considered to date from 2737 B.C.

The active ingredient in *Cannabis sativa* is delta-9-tetrahydrocannabinol (THC). The Controlled Substances Act of 1970 classified marijuana, along with heroin and LSD, as a Schedule I drug, i.e., having relatively high abuse potential and no accepted medical use. After more than a decade of decreasing use, marijuana smoking began an upward trend once more in the early 1990s, especially among teenagers, but by the end of the decade this upswing had leveled off well below former peaks of use. It currently remains the most frequently used illegal drug in the United States.

Although marijuana is relatively easy to obtain, its illegality has led to the development of "legal marijuana." Synthetic marijuana products have become popular in the last few years and have been available on the Internet since 2006. Synthetic cannabinoids JWH-018, JWH-073, and JWH-018 were developed in 1995 at Clemson University. Two other popular cannabinoids, HU-210 and CP47,497, were developed in the 1980s. They are aminoindoles. These compounds are infused into herbal preparations and sold as legal marijuana, thus the effects may be due to the herb as well as the drug. Pharmaceutical researchers and researchers in search of a cannabinoid receptor with the analgesic and inflammatory properties without the psychotropic effects have developed hundreds of compounds, many of which may be available to be used as synthetic marijuana.[29]

"K2," or "spice," refers to a series of products that are advertised and were sold legally as herbal blend incense. They contain the synthetic cannabinoid JWH-018, but may contain one or more of the following: CP-47,497, JWH-175. This preparation was a favorite among users because of its cannabis-like effects, legality, and it did not show on urine drug testing. An analysis of random samples from online sources showed that they contained mainly the mentioned drugs with few contaminants or other drugs.[30] These facts make this synthetic marijuana popular among teens. According to the American Association of Poison Control Center (AAPCC), more than 2500 calls related to "K2" were reported in 2010, compared with only 53 in 2009.

Mechanism of Action. The synthetic cannabinoids bind with the CB1 and CB2 cannabinoid neural receptors. Their mechanism of action mimics the effect of THC but with more pronounced effects. THC works on the cannabinoid receptors (CB1 in the brain and CB2 in the immune system cells). The cardiovascular responses that occur in response to THC are mediated by the autonomic nervous system. Although several mechanisms exist by which marijuana use might contribute to the development of chronic cardiovascular conditions or acutely trigger cardiovascular events, there are few data regarding marijuana, THC use, and cardiovascular outcomes.[29]

Clinical Effects. Marijuana is most often smoked but can be eaten. The effects of smoking are evident within minutes and last up to 3 hours. Tachycardia, hypertension, vasodilation, decreased intraocular pressure, and bronchodilation are associated with marijuana use. Marijuana has been linked to multiple cardiac effects, both dangerous and potentially beneficial. There have been numerous case reports of myocardial infarction associated with cannabis use.[31] Almost all of the patients reported had other risk factors such as cigarette smoking and other drug use.[32] A positive drug screen for THC may not be enough to link THC with a cardiac event, and plasma levels would be more useful to determine a potential relationship.[33] Some reports suggest there might be a beneficial effect of cannabis on the cardiovascular system.[34]

Adverse Reactions. The synthetic cannabinoids have similar effects to cannabis, but these effects can be more pronounced. Symptoms

include chest pain, acute psychomotor agitation, paranoid hallucinations, pallor, tremor, and seizures. Although not reported, there is concern about a serotonin syndrome due to the indole moiety contained in the synthetic cannabinoid.[35] The most serious complication of marijuana use reported in the literature is myocardial infarction, although this complication seems to be only with patients with a risk for MI.[36]

A recent report of three healthy teenagers who suffered MIs after use of "K2" suggests that the synthetic marijuana may have more significant cardiac effects than marijuana.[37] As mentioned, other ingredients may also be present in the synthetic form. Another recent report links "K2" with myocardial infarction[47] and seizures.[38,39]

While some studies have detailed the adverse events and emergency department presentation associated with "K2" use, it is unclear if this product is being used by persons who are unfamiliar with THC and, thus, unfamiliar with the effects, or if it is only being used by frequent THC users.[40]

ED Management. Management is supportive. If the patient complains of chest pain, acute coronary syndrome or myocardial infarction must be excluded.

Hallucinogenic Drugs

Hallucinogens have been used for centuries, most coming from naturally occurring plants. These drugs, such as psilocybin, have been extensively reviewed. LSD has been used for years and remains a popular hallucinogen. The newer drugs or those recently en vogue are discussed here.

Bromo-Dragonfly. Bromo-Dragonfly, B-Fly, or the "FLY" is a new hallucinogen on the market with no known therapeutic use. It is related to the phenethylamines and was first synthesized in 1998.[41] It has both stimulant and hallucinogenic effects. This compound was developed to study the serotonin receptors and, thus, has a chemical structure similar to serotonin. Use of this drug goes back to 2001, but has become more popular since 2005, mainly in Europe. As of this report, it is legal in the United States and the United Kingdom. It is supplied in blotter paper (imitating a familiar form of LSD), liquid, and pill form. It is usually taken orally, but can be used nasally. Because of the delay in onset of effects, repeat dosing is a problem. Hallucinogenic effects may last for 6 hours, and there have been reports of symptoms for days. This fact is most likely the reason its use is limited.

Mechanism of Action. The hallucinogenic effect of Bromo-Dragonfly is mediated by its agonist activity at the 5-HT2A serotonin receptors.

Clinical Effects. Bromo-Dragonfly can produce a hallucinogenic effect for 6 to 24 hours. It also has amphetamine-like effects.

Adverse Reactions. Nausea, headache, fever, and disorientation have been reported. Inexperienced users may have difficulty with the hallucinogenic effects of the drug, especially with its prolonged clinical effects.

ED Management. ED management is supportive.

Salvia. *Salvia divinorum*, commonly referred to as "Diviner's Sage" or "salvia," is a plant from the Mexican Lamiaceae mint family that has been known to produce hallucinogenic effects. It grows wild in the Sierra Mazateca mountain region in Mexico but, due to demand, is also cultivated in the United States. It is still legal in most of the United States and can be obtained easily on the Internet.

Mechanism of Action. The active ingredient in salvia is the non-alkaloidal hallucinogen salvinorin A, which is the primary agent for salvia's psychoactive effects and regarded as one of the most potent naturally occurring hallucinogens.[42] In 2002, researchers discovered that salvinorin A acts on the kappa opiate receptor. Other hallucinogens like LSD and psilocybin work on serotonin receptors.[43] Binding at kappa opioid receptors is known to cause neurologic effects, including sedation, analgesia, and perceptual disturbance, with the latter responsible for its hallucinogenic effects.[44] Despite its low toxicity, the increase in use is likely to result in more ED visits.

Clinical Effects. Salvia can be taken in different ways, including chewing the leaves, smoking the leaves, as a tea, or as concentrated extract administered sublingually. When smoked, the effects typically appear within 1 minute of use and last 15 minutes or less, but this varies depending on the amount used, concentration, and mode of administration.[42] Feelings of calmness for 24 hours have been reported. In surveys of users, most say they had a pleasant experience. One survey noted only 1 in 500 users sought medical treatment. Most experience a sense of well-being, visual or auditory hallucinations, out-of-body experience, and increased perception.

Adverse Reactions. The toxicity of *S. divinorum* appears low. Adverse reactions included disorientation, agitation, tachycardia, and hypertension.[45]

ED Management. No clinical trials exist for management of adverse reactions. Management is supportive. Benzodiazepines can be used for agitation.

Kratom. *Mitragyna speciosa* is a tree native to Asia and Africa. The most prevalent alkaloid present in the tree is mitragynine. The leaves can be brewed as a tea or eaten. It is used to ameliorate opioid withdrawal symptoms.[45]

Clinical Effects. Kratom leaves, when chewed, have an onset of action within 5 to 10 minutes and last about one hour. It has both stimulant and sedative effects and has been said to have effects similar to coca leaves.

Mechanism of Action. The active ingredient in kratom is mitragynine, which is responsible for its opioid effects. Mitragynine displays in vitro activity at both supraspinal opioid mu and delta receptors.[46] The mu receptor mediates analgesia, euphoria, and respiratory depression, which accounts for the analgesia activity of mitragynine, as well as its

amelioration of opiate withdrawal symptoms.

Adverse Reactions. Nausea, vomiting, and diarrhea have been commonly described among kratom users, with occasional reports of nystagmus and tremor.

ED Management. Because of its low toxicity, symptomatic treatment is appropriate.

Benzodiazepines

Phenazepam and Etizolam. Phenazepam is a benzodiazepine related to diazepam but significantly stronger. It was developed in the Soviet Union as an anxiolytic, anticonvulsant, muscle relaxant, and sedative medication. It is used illicitly in various forms around the world. In the United States, it is mixed with LSD and sold as "blotter." It is currently legal in the United States.[47] Etizolam is a benzodiazepine analogue. It works in a very similar way to benzodiazepines, although it actually has a slightly different chemical structure, as it has a thiophene ring. Etizolam is mainly prescribed to treat insomnia and anxiety disorders such as panic disorder or generalized anxiety disorder. One milligram of etizolam is roughly equivalent to 10 mg of diazepam (Valium). Both are still available via the Internet.

Mechanism of Action. Etizolam and phenazepam activate the same benzodiazepine receptor as other typical drugs of this class such as diazepam. Therefore, it binds to the GABA receptors and potentiates GABA transmission and causes sedation of the central nervous system. This is what leads to its range of therapeutic and unwanted side effects.

Clinical Effects. Both drugs have effects similar to those of benzodiazepines.

Adverse Effects. Because both drugs are stronger than Valium and other more common benzodiazepines, overdose can cause extreme sedation and respiratory arrest.

ED Management. As with most of the new drugs, there is not enough information to provide definitive therapeutic recommendations. Treatment should be supportive, with special attention to airway management. In addition to supportive measures, flumazenil may be used.

Conclusion

The ED physician will be confronted with an unending supply of new drugs of abuse, as well as drugs already in use. The Internet and popular press play a large role in the popularity, availability, and use of these drugs. As long as people seek altered states of consciousness, there will be a market for these drugs.

Because the newer "designer" drugs do not go through clinical trials, their effects and the ED management are determined by the similarity to existing, better known drugs. In addition to these new drugs, the ED physician will also be dealing with multiple drug use, which further complicates the ED evaluation and management. The management is therefore based on the presenting signs and symptoms.

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Physician CME Questions

1. The serotonin syndrome includes which of the following?
   A. hyperthermia, seizures, dysrhythmias
   B. hypothermia, increased secretions, bradycardia
   C. hypotension, pin point pupils, respiratory depression
   D. ataxia, blurred vision, confusion

2. Police bring in a 16-year-old male who was found in the street extremely agitated and uncooperative. Vital signs in the ED: BP 252/110; HR 198; RR 32; oxygen saturation on room air 88%. ECG showed tachycardia. Which of the following did this patient ingest?
   A. K2
   B. methamphetamine
   C. GHB
   D. Bromo-Dragonfly

3. A 14-year-old girl is brought to the ED by her parents because she was complaining of severe chest pain. She admits to smoking "spice." Vital signs: temp 37.2°C; HR 100; RR 15; BP 105/70; pulse ox 98%. Her physical exam is normal. The appropriate ED management is:
   A. NSAIDS for the chest pain and discharge home
   B. sedation with benzodiazepines
   C. evaluation for acute MI
   D. admission to the psychiatric unit

4. A 16-year-old is brought to the ED by EMS. She was at a party where alcohol was readily available. Vital signs are: temp 37°C; BP 115/75; P 98; RR 12; pulse ox 97%. She is unarousable but otherwise the PE is normal. Her evaluation includes normal electrolytes; drug screen negative; alcohol level 0.03. When she awakens she admits to having 2 alcoholic drinks. In addition to alcohol she probably also took:
   A. "K2"/"spice"
   B. MDMA (methylenedioxymethamphetamine)
   C. "bath salts" (mephedrone)
   D. GHB (gamma-hydroxybutyrate)

5. "Bath salts" contain which of the following drugs?
   A. mephedrone or methylenedioxypyrovalerone (MDPV)
   B. salvinorin A or mitragynine
   C. benzylpiperazine (BZP) or gamma-hydroxybutyrate (GHB)
   D. amphetamine or methamphetamine

6. The only drug listed below that is completely synthetic with no similar drugs occurring naturally is:
   A. tetrahydrocannabinol (THC)
   B. methamphetamine
   C. mephedrone
   D. BZP (benzylpiperazine)

7. GHB (gamma-hydroxybutyrate) is called the "date rape drug" because:
   A. When mixed with alcohol it induces deep sedation.
   B. It is hallucinogenic.
   C. It impairs judgment.
   D. It causes increased thirst.

8. A 16-year-old girl is brought to the ED by her friends having generalized tonic-clonic seizures. She went with her friends to a "rave party" because she was depressed and had some alcohol. She has a history of depression and is taking some medicine for it. On arrival she is having generalized seizure activity, which is treated with benzodiazepine. Her VS are temp 38.7°C, HR 140, RR 30, BP 150/90. Laboratory evaluation shows: sodium 124 mEq/L; potassium 5.3 mEq/L; bicarbonate 15; chloride 100 mEq/L; glucose 85 mg/dL; toxicology screen positive for THC; alcohol level 0.10. In addition to marijuana and alcohol, she most likely took:
   A. K2 (spice)
   B. Bromo-Dragonfly
   C. MDMA
   D. BZP

9. Ingestion of which of the following plants causes CNS stimulation?
   A. *Salvia divinorum*
   B. *Ephedra sinica*
   C. *Cannabis sativa*
   D. *Amanita phalloides*

10. MDMA-associated hyperthermia can cause any of the following *except*:
    A. rhabdomyolysis
    B. acute kidney injury (AKI)
    C. hyperkalemia
    D. hypernatremia

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Drugs of Abuse 2012 Update

Serotonin Syndrome (Hunter Criteria)

Patient has taken a serotonergic agent and has one of the following:

- Spontaneous clonus
- Inducible clonus and agitation or diaphoresis
- Ocular clonus and agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia
- Temperature above 38°C and ocular clonus or inducible clonus

Complications of Hyperpyrexia Syndrome

- Delirium and agitation
- Seizures
- Rhabdomyolysis
- Hyperkalemia
- Arrhythmias
- Metabolic acidosis
- Myocardial ischemia
- Cerebral ischemia
- Cerebral edema
- Acute kidney injury
- Pulmonary edema
- Acute respiratory distress syndrome
- Hepatotoxicity
- Coagulopathy
- Shock necessitating vasotropic/inotropic support

Adapted from: Grunau BE, Wiens MO, Brubacher JR. Dantrolene in the treatment of MDMA-related hyperpyrexia: A systematic review. *CJEM* 2010;12:435-442.

Supplement to *Pediatric Emergency Medicine Reports*, December 2012: "Drugs of Abuse 2012 Update." *Author:* **Robert A. Felter, MD, FAAP, CPE, FACPE,** Attending Physician, Emergency Medicine and Trauma Center, Professor of Clinical Pediatrics, Georgetown University School of Medicine, Washington, DC.

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The Practical Journal of Pediatric Emergency Medicine

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