Emerging Drugs of Abuse

Michael E. Nelson, MD, MS[a,b,*], Sean M. Bryant, MD[b], Steven E. Aks, DO[b]

KEYWORDS

• Synthetic cathinones • Synthetic cannabinoids • Phenethylamines • Piperazines • Herbal drugs of abuse • Prescription drug abuse • Managing new drug exposures

KEY POINTS

- Emerging drugs of abuse are forever changing and involve manipulation of basic chemical structures to avoid legal ramifications.
- The individual names and chemical formulations of emerging drugs of abuse are not as important as a general understanding of the classes of drugs.
- Most of the synthetic new drugs of abuse result in psychoactive and sympathomimetic effects.
- Management generally involves symptom-based goal-directed supportive care with benzodiazepines as a useful adjunct.

INTRODUCTION

Remaining abreast of emerging drugs of abuse continues to challenge emergency practitioners (EPs). As law enforcement agencies classify certain drugs as illegal, street pharmacists rapidly adapt and develop new congeners of old drugs for distribution and use. It is essential that EPs have a solid foundation in the general classes of drugs of abuse. Many of the newer drugs have similar effects, and respond well to meticulous and aggressive supportive management. Sources of information and surveillance should be available so that EPs remain knowledgeable of current trends. Poison centers, along with local public health officials, should be important sources of current information. Internet sites, social media, and search engines may be additional tools for drugs of abuse trends.[1,2]

Legal highs present an ongoing issue. These products are sold in head shops, the Internet, and other sources.[3] Bath salts (cathinones, mephedrone, and others) and synthetic cannabinoids are two useful examples of the problem of legal highs and

[a] Department of Emergency Medicine, NorthShore University Health System, 2650 Ridge Avenue, Evanston, IL 60201, USA; [b] Department of Emergency Medicine, John H. Stroger Jr. Hospital of Cook County, Toxikon Consortium, Illinois Poison Control Center, 1900 West Polk Street, 10th Floor, Chicago, IL 60612, USA

* Corresponding author. Department of Emergency Medicine, John H. Stroger Jr. Hospital of Cook County, Toxikon Consortium, Illinois Poison Control Center, 1900 West Polk Street, 10th Floor, Chicago, IL 60612.

E-mail address: menelson4@gmail.com

Emerg Med Clin N Am 32 (2014) 1–28

http://dx.doi.org/10.1016/j.emc.2013.09.001 **emed.theclinics.com**

0733-8627/14/$ – see front matter

are discussed later. These substances tend to be slightly altered chemicals derived from other known drugs of abuse. They were easily obtained on the Internet and in tobacco head shops, and were finally banned once public health and law enforcement officials identified these compounds and adapted laws. Recent legislation shows that authorities can act quickly to implement important public health laws. The Synthetic Drug Abuse Prevention Act of 2012 included synthetic cannabinoids in the schedule I category, which subsequently diminished their availability considerably.[4]

One article nicely summarizes the cycle of one drug of abuse.[5] Ecstasy (MDMA, 3,4-methylenedioxy-*N*-methylamphetamine) has been abused for several decades. Its street use was complicated by adulteration and substitution. However, there has been a resurgence of this drug as "Molly," which is touted to be a pure form of ecstasy. Much of this street information is unreliable, but the fact that Molly appeared in the fashion section of a notable newspaper is remarkable.

PRESCRIPTION DRUG ABUSE EPIDEMIC

Another major perspective for EPs to maintain is the current prescription drug epidemic. Beginning in 2004, prescription opioids have outstripped street heroin and cocaine as causes of death.[6] Physician prescriptions can and are being used as emerging drugs of abuse. Opioids and benzodiazepines are frequent diversion targets.[6,7] Patients prescribed these medications and other controlled substances such as medications for attention deficit hyperactivity disorder (ADHD) should be screened for at-risk substance abuse.[8]

Most physicians are aware of prescription-monitoring programs and can use this as a tool to detect diversion and to identify multiple prescriptions of controlled substances.[9,10] Although it is controversial whether prescription-monitoring programs are effective in reducing rates of drug overdose mortality, they are an important tool to prevent the inappropriate use and diversion of these medications.[9]

Unfortunately, the problem expands far beyond the prescription drug arena. There is widespread over-the-counter drug abuse and misuse.[11] Weight-control drugs and laxatives are just two such examples. Further attention on how a product is sold, such as behind-the-counter (BTC) status, is appropriate to assure age-appropriate use.[11]

Performance-enhancing drugs are and will continue to be emerging drugs of abuse. The incentives to perform at high levels are profound and with increasingly sophisticated techniques of drug detection, it is logical that this will be an evolving arena. These substances are widely available on the Internet.[12] The World Anti-Doping Agency (WADA) modifies its prohibited list on an annual basis in response to this ongoing issue.[13] This discussion, however, is immense in itself and beyond the scope of this article.

Not only are performance-enhancing drugs abused, but so too are drugs that are used to improve appearance. Examples include weight loss and melanotan products. Melanotan products are Internet-purchased substances used to improve tanning, and have been reported to cause significant sympathomimetic signs and symptoms, along with rhabdomyolysis and renal dysfunction.[14]

In addition to the substances covered in this article, there are numerous other examples of drugs of abuse that continue to emerge and evolve. Methoxetamine, a ketamine analogue, has become a drug of abuse. It carries the purported advantage over ketamine of being less toxic to the urologic system, although animal studies call this into question.[15] Krokodil, or desomorphine, is a drug of abuse that is typically used when heroin or poppy straw is in short supply. Significant abuse has been

described in Ukraine.[16] Even common substances found in convenience stores can be misused. A recent example includes the abuse of energy drinks. These beverages can contain caffeine, taurine, niacin, and other substances. Some individuals coingest these drinks with ethanol, and this pattern of misuse has resulted in mixed toxic effects.[17]

As the number of potential substances for abuse is immense and beyond the scope of a single article, the following sections cover the most significant recent and emerging drugs of abuse. These substances include the synthetic cannabinoids, bath salts, amphetamines and phenethylamine substances, piperazines, and emerging herbs of abuse. General toxicity as well as overall supportive measures are also reviewed.

SYNTHETIC CANNABINOIDS

Introduction

Cannabis is one of the most widely used illicit substances worldwide and in the United States, possession and distribution carry legal ramifications.[18] In the last decade, synthetic cannabinoids (SCs, also referred to as synthetic cannabinoid receptor agonists) gained popularity as a legal alternative to achieve euphoric effects similar to cannabis. These products were sold at head shops, convenience stores, and on the Internet as herbal incense or air fresheners, and were marketed as not for human consumption.[19,20] The most common street names for SCs are K2 and Spice.[21] They did not originally come under initial legal regulations from the US Federal Controlled Substances Act because of their structural dissimilarity to Δ^9-tetrahydrocannabinol (Δ^9-THC). In addition, many other biological herbs besides SC are contained in these products.[21–23] Packaging notoriously contains minimal information regarding the chemical composition of the plant products and no standard exists for the ingredients or concentrations.[24] SCs are typically sold in metal foil sachets as a mixture of dried vegetable matter with the SC substance sprayed onto the herbal mixture.[25] SCs are comprised of many substances (**Box 1**), with dozens of different assigned street names (**Box 2**).

History and Epidemiology

The first synthetic Δ^9-THC was produced in 1967, and in 1985, dronabinol (Marinol) was approved as an antiemetic in the United States.[21] Subsequently, other SCs including nabilone (Cesamet) and nabiximols (Sativex) were used for refractory emesis in chemotherapy, as adjuncts for neuropathic pain, and for anorexia in patients with

Box 1
Various synthetic cannabinoids

JWH-015	(C8)-CP-47,497
JWH-018	HU-210
JWH-073	CP-55,490
JWH-200	AM-2201
JWH-081	WIN-48,098
JWH-122	WIN-54,461
JWH-210	WIN-55,212-2
JWH-250	XLR-11
JWH-398	UR-144
CP-47,497	—

Box 2
Common street/brand names for substances containing synthetic cannabinoids

Spice	Bombay blue
K2	Blaze
Happy tiger incense	Bliss
Spice gold	Chill zone cherry
Spice silver	Chaos mint
Spice diamond	Clover spring
Spice Egypt	Fake weed
Spice arctic synergy	Genie
SpicyXXX	Eclipse
Smoke	Krypton
Banana cream nuke	Moon rocks
Aroma	Mr Smiley
Aztec fire	Sensation vanilla
Black mamba	Yucatan fire
Blueberry posh	Zohai

AIDS.[21,26,27] Another classic cannabinoid is HU-210, which is structurally similar to Δ^9-THC, but much more potent.[20,21] Other nonclassic cannabinoids, called cyclohexophenols (CP) and aminoalkylindoles (AAIs), were developed in the 1960s to 1980s and have similar clinical effects as Δ^9-THC.[20,21,24,28,29] The SCs fall into seven major structural groups: naphthoylindoles (eg, JWH-015, JWH-018, JWH-073), naphthylmethylindoles, naphthoylpyrroles, naphthylmethylindenes, phenylacetylindoles (eg, JWH-250), cyclohexophenols (eg, CP-47,497), and classic cannabinoids.[24,25,30]

John William Huffman, a chemist at Clemson University and namesake of many SCs (JWH compounds), synthesized multiple AAIs with varying degrees of affinity for cannabinoid receptors (CBRs).[19,31–33] Of the various JWH compounds created, the pharmacology is similar to Δ^9-THC, JWH-018 is reported to have the greatest potency at CBRs.[21,29,33–35] JWH-018 was the first and most widely reported substance uncovered in SCs.[24,34–36] These SC-containing products emerged in European markets in 2004 and in the United States in 2008, with the first cases reported to US poison centers in 2009.[22,36,37] In November 2010, the US Drug Enforcement Administration designated five popular SCs (JWH-018, JWH-073, JWH-200, CP-47,497, and a C8 homologue of CP-47,497) temporarily schedule I status effective March 2011 "to avoid an imminent hazard to the public safety."[38]

A unique property of SC products is the frequently changing chemical composition and development of new derivatives, perhaps as a means to avoid legal ramifications. Regardless, these products are lipid-soluble, nonpolar, and volatilized chemicals that mimic the action of Δ^9-THC.[20] This variable composition of SC products makes development of standardized tests and confirmatory analysis in patients difficult.[20,39] Furthermore, because of this variability, obtaining pharmacologic and pharmacokinetic profiles of SCs with adverse effects is more difficult.[20] Hundreds of different SCs may be incorporated into the various constituents being used.[30]

The exact prevalence of societal SC use is unknown. According to 2012 data, SC use in US 12th graders remained constant from 2011 to 2012 at an annual prevalence rate of 11.3%, but had a low level of perceived risk in 23% to 25% of respondents.[40] Even among athletes tested in 2010, JWH-018 and JWH-073 metabolites were detected in 4.5% of samples.[41] Nearly 11,000 exposures to SC have been reported to US poison centers between 2009 and mid-2012, with overall reported exposures increasing until July 2011. Since then, reported exposures to SCs have remained

increased at roughly 500 to 700 per month, higher than exposures to synthetic cathinone.[37] The most common reason for use is intentional abuse, and inhalational exposure predominates.[37,42,43] Most SC users tend to be male and in their teens to early 20s.[24,37,42–44] More severe clinical effects have been observed in SC users than in marijuana users; up to 7.3% of exposures were life-threatening.[42,43] In a recent large global sample of nearly 15,000 participants, 17% reported SC use, with 99% of these individuals having used natural cannabis.[44] During the increase in popularity of SCs, EPs had little knowledge of common names for SC products, with most of their knowledge originating from nonmedical sources. Eighty percent of clinicians felt unprepared to care for patients with SC poisoning in the emergency department (ED).[45]

Pharmacology

Cannabinoid receptors are diverse with a large number of biological targets. CB_1 G-protein coupled receptors are abundant in the brain and modulate γ-aminobutyric acid and glutamate neurotransmission. A high density of CB_1 receptors exists in the basal ganglia. CB_2 receptors are typically found in the peripheral tissues (spleen and immune cells) and possibly mediate immunosuppression, but may also be present in the central nervous system (CNS).[20,30,46] CBRs are also complexed with other receptors, including opioid and dopamine receptors. Cannabinoids themselves can modulate various receptors including acetylcholine, opioid, serotonin, glycine, glutamatergic, and nuclear peroxisome proliferation-activated receptor α receptors.[20,47] Cannabinoids' main metabolic pathway occurs through oxidation via the hepatic cytochrome P450 pathway and conjugation with glucuronic acid to achieve renal excretion.[48]

Synthetic cannabinoids have varying degrees of affinity for CBRs.[49] The potency of HU-210 is reported to be 100 to 800 times greater than Δ^9-THC at CBRs and CP-47,497 and its C8 homologue is 30 times more potent.[21,49] In addition, different SCs have greater affinity for CB_2 receptors, such as JWH-015 and JWH-133.[21] Because of this wide variability, the pharmacodynamics and kinetic profiles of many SCs are unknown.[20,30] One of the more common SCs, JWH-018, reaches peak serum concentrations rapidly via inhalation, has a short half-life, and is five times more potent than Δ^9-THC. This pharmacologic profile, however, cannot be extrapolated to all SCs.[50,51] SC users report a quicker peak and shortened duration of effects compared with natural cannabis.[44] Furthermore, unlike Δ^9-THC, SC metabolites have varying degrees of activity (agonistic, antagonistic, or neutral) at CBRs, potentially explaining the mixed effects observed clinically.[20,51,52] Activity at receptors other than CBRs for SCs is unknown and implications are undetermined, but the potential exists given the many receptors where natural cannabinoids exert their effects.[20,47]

Clinical Effects

A wide variety of clinical effects have been reported, from mild symptoms to severe sympathomimeticlike effects and seizures (**Table 1**). Because of the variability of SC concentration and substances, recreational use can result in unintentional overdose.[22] The most common findings reported to poison centers include tachycardia, agitation, vomiting, drowsiness, confusion, hallucinations, hypertension, dizziness, and chest pain.[42,43]

A multitude of psychoactive SC effects are described and range from a desired euphoria to severe anxiety and psychosis.[20,22,24,53] A case series of 10 otherwise healthy men developed auditory hallucinations, visual hallucinations, paranoid delusions, odd affect, disorganized speech and behavior, with suicidal ideation lasting days to months after smoking SC products.[54] Spice use has also triggered an acute

Table 1
Clinical effects of synthetic cannabinoids

System	Effects
CNS	Seizures, agitation, anxiety, irritability, sedation, confusion, paranoia, psychosis
Cardiovascular	Tachycardia, dysrhythmia, chest pain, myocardial infarction, elevated blood pressure
Gastrointestinal	Nausea, vomiting
Renal	Acute kidney injury
Metabolic	Hypokalemia, hyperglycemia
Ophthalmologic	Mydriasis, conjunctivitis
Other	Hyperthermia, tolerance, withdrawal, dependence

exacerbation of cannabis-induced recurrent psychosis, paranoid delusions, and an enhanced risk of psychosis in susceptible individuals.[53,55,56] Anxiety-like reactions can occur, necessitating treatment in the ED.[56,57]

Synthetic cannabinoid use is also associated with additional CNS effects including confusion, tremors, sedation, memory changes, and seizures.[20,36,53,57–60] Although rare for natural cannabis, the mechanism of action for seizure induction with SC is still unknown, but may occur through release of excitatory neurotransmitters or a decrease in inhibitory neurotransmitters.[36,58] This effect may be dose related.[36]

Cardiovascular effects commonly include hypertension and tachycardia.[36,42,43] Cases have involved refractory supraventricular tachycardia requiring electrical cardioversion.[36] Chest pain with electrocardiogram (ECG) changes typical for ST elevation myocardial infarction and increased troponin levels have been observed in teenagers despite normal coronary arteries.[61]

Additional effects reported include gastrointestinal upset with nausea and emesis.[42,58,62,63] Ophthalmologic examination generally reveals normal to mydriatic pupils and injected conjunctiva.[22,57,62] Xerostomia and flushing can occur with development of hyperthermia.[21,22,50] Appetite changes have been reported including both increased and decreased appetite.[53] A case of diffuse pulmonary infiltrates with acute respiratory distress syndrome (ARDS) has been attributed to chronic SC use.[64] Metabolic changes may not be observed in many cases, but have included hypokalemia, hyperglycemia, and leukocytosis.[21,36,57,58,62–65] Recent reports from several states include cases of acute kidney injury requiring hemodialysis from SC use (in particular the SCs XLR-11, UR-144, AM-2201).[63] According to voluntary, spontaneous reporting to the National Poison Data System (NPDS) from 2011, a total of 4 deaths were related to THC homologues. One ingestion was coded as “probably responsible” for the death and described a 19-year-old man with postmortem urinalysis positive solely for metabolites of JWH-018.[66]

Chronic effects of SC use are unknown.[20] Chronic cannabis use has been associated with neuropsychological decline with impaired concentration and greater IQ decline.[67] Cannabis influences emotional and sensory processing and SCs may have similar cognitive effects.[20] The chronic psychiatric symptoms or effects are unknown, but SCs have triggered psychotic symptoms with suicidal ideations.[54,55] Natural cannabis withdrawal symptoms have been described and include insomnia, anxiety, irritability, malaise, myalgias, shakiness, nausea, vomiting, and drug craving for 1 to 2 weeks.[68,69] Chronic use of SCs can result in a similar withdrawal syndrome on cessation.[70,71]

Among users, natural cannabis is preferred to SCs by an overwhelming majority because of the more negative effects produced by SCs, including paranoia and hangover effects.[44] Consumers of SCs also self-reported concomitant use of other substances including alcohol, cocaine, benzodiazepines, amphetamines, MDMA, ketamine, and mephedrone.[44] Mixed ingestions may create complex clinical situations and complicate care.

Testing and Imaging

No specific testing is recommended or indicated for synthetic cannabinoid ingestion. Laboratory testing and imaging should be directed toward clinical observations and symptoms as needed. Routine qualitative drug testing of urine for Δ^9-THC is generally negative.[22,36,57–60] SCs can, however, be detected by gas chromatography-mass spectrophotometry (GC-MS) or by liquid chromatography-tandem mass spectrometry (LC-MS/MS).[20,22,24,30,39,50,60] Independent laboratories have commercial tests for both the SC product and for SCs in human blood and urine samples.[72] These tests generally are time-consuming, must be sent to referral laboratories, and the results are not readily available for the treating EPs.

Treatment

No specific antidote exists for SCs.[30] Treatment consists of symptom-based goal-directed supportive care with patient education and abstinence from further use. Specific treatment options are discussed in greater detail in the section on management principles.

Summary

SCs are a diverse group of heterogeneous compounds with a wide variety of clinical effects. Their use has increased over the past decade, as they have been viewed as a legal and safe alternative to natural cannabis.[65] Although true prevalence rates are unknown, young men tend to be the highest risk group of individuals to use SCs. In addition, diverse SCs exist with different potency at CBRs and potentially other receptors. The clinical presentation of SC intoxication varies greatly but generally involves tachycardia, hypertension, alteration in cognition and mood, and potentially seizures. No specific antidote exists and patients should be treated based on symptoms. Despite public awareness and legal action, SC use has remained popular.[30]

SYNTHETIC CATHINONES (BATH SALTS)

Introduction

Synthetic cathinones, commonly sold as bath salts, have recently emerged as a popular drug of abuse. They were marketed as legal highs similar to SCs and "not for human consumption" to avoid legal and regulatory oversight.[30] They are sold at head shops and on the Internet similar to SCs. Cathinone occurs naturally in the leaves of the khat plant (*Catha edulis*). Khat leaves contain phenylalkylamine compounds (cathinone, cathine, and norephedrine) structurally related to amphetamine and noradrenaline and produce stimulant effects.[73,74] Cathinone, however, seems to be the main constituent responsible for the amphetaminelike euphoria.[75] Synthetic cathinones are derivatives of cathinone with various chemical alterations affecting pharmacokinetics and pharmacodynamics.[30] They comprise many various substances (**Box 3**) and are referred to by a wide variety of street names (**Box 4**).

Box 3
Common synthetic cathinones

Methcathinone	Ethylone
Mephedrone	Methedrone
Methylenedioxypyrovalerone (MDPV)	Naphyrone
Methylone	3-Fluoromethcathinone
Butylone	4-Fluoromethcathinone (flephedrone)
Brephedrone	α-Pyrrolidinovalerophenone
Pyrovalerone	3,4-Methylenedioxy-α-pyrrolindinopropiophenone (MDPPP)
Dimethylecathinone	—
Ethcathinone	—

History and Epidemiology

Individuals have chewed khat leaves to obtain the stimulant effects of natural-occurring cathinone (*S*-(−)-2-amino-1-phenyl-1-propanone) for centuries.[30] Chewing natural khat remains local to areas where it is grown, particularly in Middle Eastern nations such as Yemen and in East African nations such as Somalia and Ethiopia, as only the fresh leaves contain the active cathinone.[75,76] Khat chewing itself has reportedly been associated with higher risk of stroke and death.[76] The first synthetic cathinone, methcathinone, was created in 1928, with mephedrone soon following in 1929.[74,77] Shortly after, the Advisory Committee on the Traffic in Opium and Other Dangerous Drugs of the League of Nations discussed the potential of khat and cathinone as a health hazard.[73] In the 1930s and 1940s, methcathinone was used as an antidepressant in the Soviet Union and subsequently has been used recreationally.[78] In the 1970s, pyrovalerone was studied for treating fatigue and obesity, but the study had to be discontinued because users developed dependency and abuse.[74] The cathinone derivative chloro-α-t-butylaminopropiophenone was patented in 1974 and currently is marketed as bupropion (Wellbutrin, Zyban) for prescription use to treat depression and nicotine craving.[74,79] Cathinone abuse outbreaks occurred in the United States and Europe in the 1990s, and in 1993 methcathinone was designated as a schedule I substance.[30,78,80]

Around the same time as the SC epidemic, synthetic cathinones also gained popularity. First reports in Internet drug chat forums of mephedrone use occurred in 2007 and were detected by a web-mapping research group in 2008.[81] The increased popularity of mephedrone and other synthetic cathinones was driven by lack of availability or poor purity of other recreational stimulants such as cocaine and MDMA combined with availability over the Internet and no legal regulation.[82] US poison centers began receiving calls related to bath salts in 2010 with a peak in volume in mid-2011.[37]

Box 4
Common street names for synthetic cathinones

Khat	Meow meow
Bath salts	MCAT
Ivory wave	Bubbles
Vanilla sky	Cloud 9
White rush	Explosion
White lightning	Impact
White dove	Energy-1

The exact prevalence of use of synthetic cathinones in society is unknown. Synthetic cathinone use in US 12th graders in 2012 had an annual prevalence rate of 1.3% (compared with 11.3% for SC).[40] A survey of 1006 secondary and university school students in the United Kingdom reported 20.3% of respondents used mephedrone with 4.4% reporting daily use. Sixty-six percent of individuals surveyed found mephedrone easily obtainable.[82] A survey of 2700 UK dance club frequenters reported 41.3% used mephedrone, 10.8% used methylone, and 1.9% used methylenedioxypyrovalerone (MDPV).[83] A 1-year review of data from 9 US Midwest poison centers relating to bath salts involved 1633 patients. Males (68%) dominated and most (54%) were younger than 30 years.[84] Synthetic cathinone users tend to be younger males, the same demographic as SC users.

In the United States, calls to poison centers related to bath salts totaled 303 in 2010, 6062 in 2011, 2656 in 2012, and 450 in the first 5 months of 2013. The number of calls thus far in 2013 is nearly one-third of the number during the same time period in 2012 (450 calls compared with 1304 calls).[85] An increase in call numbers occurred in June 2011 and again in June 2012 for unclear reasons. From September 2012 to May 2013, calls to poison centers regarding bath salts have averaged roughly 93 per month.[85] By comparison, calls to poison centers regarding synthetic marijuana during the same time period have averaged 240 calls per month.[86]

Legislative measures have been taken against synthetic cathinones to address these once legal highs. In April 2010, the Misuse of Drugs Act classified mephedrone and other similar substances as Class B substances.[87,88] This legal action caused the price of mephedrone to double in the United Kingdom and increased purchasing from street dealers as presumably Internet purchasing was limited.[87] In September 2011, the US Drug Enforcement Agency (DEA) temporarily scheduled 3 synthetic cathinones (mephedrone, methylone, and MDPV) as schedule I.[89] The Synthetic Drug Abuse Prevention Act of 2012 extended the schedule I status of various SCs and phenethylamines including MDPV and mephedrone.[90] Calls to US poison centers for bath salts decreased from nearly 500 in September 2011 to just over 200 in November 2011.[85]

Pharmacology

Synthetic cathinones are β-ketophenethylamines structurally similar to amphetamines and catecholamines but with subtle variations that alter chemical properties and potency.[30,88] The ketone on the β-carbon of the phenethylamine constituent leads to increased polarity with reduction in CNS penetration.[88] This property may lead to higher dosing with more profound adverse peripheral effects.[88,91] The serum concentration of synthetic cathinone alone cannot determine the toxicity observed.[92]

Many routes of administration occur for bath salts. Most commonly, synthetic cathinones are insufflated (snorting) or ingested orally.[84,93,94] Intravenous, intramuscular, and rectal routes of administration also occur.[94,95] Duration of action, dosing, and time of onset of symptoms can vary with routes of administration.[94]

Limited pharmacokinetic data on synthetic cathinones are available.[30,74,91,96] Each synthetic cathinone has variable effects on neurotransmitters (serotonin, dopamine, and norepinephrine), with differing degrees of potency. The ability to modulate these monoamines creates psychoactive and sympathomimetic effects.[74,91,96,97] Synthetic cathinones inhibit monoamine uptake transporters and cause release of intracellular stores of monoamine neurotransmitters, leading to increased amounts of these neurotransmitters in the synapse.[96,98,99]

Understanding of metabolism is also limited, but animal models provide some principles. Metabolism of mephedrone generally occurs through phase I pathways with

generation of multiple metabolites through N-demethylation to the primary amine, reduction of the ketone, and oxidation of the totyl group into its corresponding alcohol and carboxylic acid.[74,91,100,101] In addition, various hepatic cytochromes (CYPs) are involved in the demethylation process of MDPV, including CYP1A2, 2D6, and 2C19.[102] Many phase II metabolites of MDPV are also possible thus providing a complex process for metabolism.[102]

Clinical Effects

Cathinones create amphetaminelike sympathomimetic effects with tachycardia, hypertension, and euphoria.[75,103] The degree of hyperadrenergic effects varies based on the substance and amount ingested. Many clinical effects are possible (**Table 2**). The most common adverse effects reported involve the cardiac, neurologic, and psychiatric systems.[74] The most common clinical findings reported to poison centers include agitation, tachycardia, hallucination, hypertension, confusion, mydriasis, tremor, and fever. Additional serious effects reported include rhabdomyolysis, renal failure, seizures, and death.[84,93,104]

Cardiovascular effects are related to the stimulant effect of cathinones. Common signs and symptoms include chest pain, palpitations, hypertension, and tachycardia.[84,93–95] Mephedrone reportedly caused ECG changes, with ST segment elevation and myocardial inflammation.[105] Synthetic cathinones can potentially result in fatal cardiac dysrhythmias.[106]

Psychoactive and CNS effects most commonly involve agitation and aggression.[84,93] Many reports exist that detail psychosis and excited delirium with various synthetic cathinones.[107–111] Visual, auditory, and tactile hallucinations can occur.[108,109] Patients may become severely agitated and display violent behavior that requires physical or chemical restraint.[107] Additional findings include confusion, dysphoria, delusions, insomnia, nightmares, changes in concentration, and altered mental status.[83,94] Seizures are one of the most severe CNS effects that occur.[84,112]

Additional effects observed mimic stimulant-like symptoms with euphoria, talkativeness, desire to move, bruxism, insomnia, and reduced appetite.[113] Gastrointestinal effects include nausea, vomiting, abdominal discomfort, and xerostomia.[94] Ingestion of methylone and butylone resulted in a case of serotonin syndrome, disseminated intravascular coagulation (DIC), ARDS, and death.[114] Metabolic abnormalities have been observed, including acidosis and hyponatremia.[95,111,112] Compartment syndrome

Table 2
Clinical effects of synthetic cathinones

System	Effects
Psychiatric	Agitation, aggression, confusion, anxiety, insomnia, dysphoria, hallucinations, paranoia, delusions
CNS	Altered mental status, hyperreflexia, nystagmus, tremors, seizures
Cardiovascular	Tachycardia, hypertension, myocarditis, chest pain
Gastrointestinal	Abdominal pain, nausea, vomiting, xerostomia
Renal	Acute renal failure
Metabolic	Hyponatremia, acidosis
Ophthalmologic	Mydriasis, blurred vision
Other	Hyperthermia, diaphoresis, body odor, bruxism, epistaxis, rhabdomyolysis

has been reported.[115] Further serious effects include renal dysfunction, rhabdomyolysis, hyperthermia, and multiorgan system failure.[110,115,116] Drug-induced hyperthermia has historically been associated with poor neurologic outcomes and increased mortality.[117] Unfortunately, multiple deaths related to various synthetic cathinones are evident.[92,104,106,110,111,114,118–120]

The long-term effects of synthetic cathinone use are unknown. MDPV users reported tolerance, with consumption of higher doses.[96] Nearly 25% of mephedrone users reported a persistent desire to use and would continue to use despite physical and psychological problems, indicating a compulsion.[113] Fifty-six percent of mephedrone users reported at least one undesired effect with use.[82] Discontinuation of mephedrone has led to withdrawallike symptoms with nasal congestion, tiredness, insomnia, and impaired concentration.[113] Additional withdrawal syndromes have been self-reported with MDPV and methcathinone.[96] Nearly 30% of mephedrone users involved in the dance music scene had indicative findings of stimulant dependence.[113] Serotonergic and dopaminergic neuron toxicity in has been demonstrated in rodent models with methcathinone.[121] In humans, abstinent methcathinone users had decreased dopamine transporters on positron emission tomography scans similar to methamphetamine users and patients with Parkinson disease, suggesting the potential risk for long-term neuropsychiatric problems.[122]

Testing and Imaging

No specific testing is recommended or indicated for synthetic cathinone ingestion. Laboratory testing and imaging should be directed toward clinical observations and symptoms as needed. Despite the structural similarity to amphetamine, routine urinary qualitative drug testing and enzyme immunoassays for amphetamines are generally negative.[30,95,96,107,110,116,123] False-positive assays for methamphetamine may occur with mephedrone.[118] Synthetic cathinones and metabolites can be detected by GC-MS, LC-MS, or LC-MS/MS.[30,100–102,124] Independent laboratories have commercial tests for both the synthetic cathinone product and human blood and urine samples.[125] These tests generally are time consuming, must be sent to the referral laboratories, and results are not readily available for treating EPs.[114] Correlation of drug concentrations with observed clinical effects is not well defined or understood.[74]

Treatment

No specific antidote exists for synthetic cathinones.[30,74,111] Treatment consists of symptom-based goal-directed supportive care with patient education and abstinence from further use. The most common treatment provided for synthetic cathinones reported to poison centers is benzodiazepines.[84,104] Specific treatment options are discussed in greater detail in the section on management principles.

Summary

Synthetic cathinones are a broad group of compounds with amphetaminelike effects. Their use has increased over the past decade because they were marketed as legal highs. Many synthetic cathinones exist with variable potency but mainly affect monoamine neurotransmitters, resulting in sympathomimetic signs and symptoms. No specific antidotes exist, and treatment should be focused mainly on supportive care. Despite numerous reports of adverse events and legislative efforts, synthetic cathinone use remains popular.

OTHER PHENETHYLAMINES (2C DRUGS)

Introduction

The basic chemical structure of phenethylamine is shared among catecholamines, amphetamines, synthetic cathinones, and many other drugs.[91,126] Another class of synthetic phenethylamines abused for recreational highs are the 2C class of drugs; the name relates to the two carbons between the benzene ring and the terminal amine group.[126] Alexander T. Shulgin has often been credited with the discovery of various 2C drugs and the father of MDMA after the publication of his book *PiHKAL, A Chemical Love Story*.[127,128] The PiHKAL acronym stands for "Phenethylamines I Have Known and Loved."[128] In this text, Shulgin describes the synthesis, production, and dosages of various phenethylamines.[127] Various substitutions of the base phenethylamine structure can alter its pharmacologic and clinical effects, creating a vast array of chemical derivatives (**Table 3**).

The true prevalence of 2C and other phenethylamine use is unknown.[129] A survey of UK dance club frequenters reported 17.6% used 2C-B and 11.2% used 2C-I.[83] 2C-B was present in roughly 3% of drug materials analyzed in Spain between 2006 and 2009, and generally comes in a tablet or powder form.[129] Individuals that seek ecstasy at dance raves and other music festivals may inadvertently be exposed to 2C drugs as contaminants or MDMA substitutes.[130–132] These substances can be purchased on the Internet and can be listed as research chemicals.[132] As with SC and synthetic cathinones, 2C users tend to be younger males and may have a history of polydrug use.[129,132,133]

Many 2C substances are listed as schedule I substances.[90] Newer phenethylamine compounds, however, are continuously being designed and introduced to evade existing legislation and regulatory oversight.[130] This challenges treating providers in terms of being aware of new street names for these drugs.

Pharmacology

Complete pharmacologic and pharmacokinetic profiles of all the 2C drugs are unknown. Little modification, however, is needed to the basic phenethylamine structure

Table 3
Selected 2C phenethylamine drugs

2C-B	4-Bromo-2,5-dimethoxyphenethylamine
2C-B-Fly	8-Bromo-2,3,6,7-benzo-dihydro-difuran-ethylamine
2C-C	4-Chloro-2,5-dimethoxyphenethylamine
2C-D	4-Methyl-2,5-dimethoxyphenethylamine
2C-E	4-Ethyl-2,5-dimethoxyphenethylamine
2C-F	4-Fluoro-2,5-dimethoxyphenethylamine
2C-G	3,4-Dimethyl-2,5-dimethoxyphenethylamine
2C-I	4-Iodo-2,5-dimethoxyphenethylamine
2C-I-Fly	8-Iodo-2,3,6,7-benzo-dihydro-difuran-ethylamine
2C-N	4-Nitro-2,5-dimethoxyphenethylamine
2C-P	4-Propyl-2,5-dimethoxyphenethylamine
2C-SE	4-Methylseleno-2,5-dimethoxyphenethylamine
2C-T	4-Methylthio-2,5-dimethoxyphenethylamine
2C-T-2	4-Ethylthio-2,5-dimethoxy-β-phenethylamine

to create significant alterations in neurochemical actions.[91] Frequently, the fourth carbon position on the benzene ring is substituted to create a different compound (see **Table 3**). Furthermore, by making alterations to the substituents at the second, third, fifth, and sixth positions of the aromatic ring, even more compounds can be created (eg, Fly compounds). Most of the 2C drugs show affinity for serotonin receptors, in particular 5-hydroxytryptamine 2 receptors with variable action at receptor subtypes.[134] In addition, 2C-B has α_1-adrenergic receptor agonistic properties.[134,135] Some 2C drugs inhibit reuptake of dopamine, serotonin, and norepinephrine.[99]

Metabolism of 2C drugs occurs via O-demethylation with oxidative deamination to a corresponding acid or reduction to a corresponding alcohol.[134,136–138] Deamination mainly occurs via monoamine oxidase (MAO). As an important consequence of this metabolism, 2C drugs may create drug interactions with MAO inhibitors.[138] 2C drugs tend to have a higher affinity for MAO-A than for MAO-B.[138] Hepatic cytochrome P450 enzymes, in particular 2D6, also play a role in metabolism.[136]

Clinical Effects

Phenethylamines create a clinical picture of both stimulatory and hallucinogenic effects.[91,126] Signs and symptoms observed may include hallucinations, nausea, vomiting, dizziness, diarrhea, headaches, body aches, depression, and confusion.[132] 2C-B use resulted in a case of diffuse cerebral vasculopathy likely from vasospasm.[139] 2C-I ingestion led to reported recurrent seizures and serotonin syndrome with hyperthermia.[140] A case series of 10 patients using 2C-E displayed sympathomimetic and neurologic symptoms with tachycardia, hypertension, euphoria, agitation, psychosis, and hallucinations. Other effects seen with serotonergic and sympathomimetic toxicity can also be observed. One patient experienced fatal cardiac arrest one hour after snorting 2C-E.[133] 2C-E was reported as "undoubtedly responsible" for the death of a 19-year-old man in 2011.[66] Other various 2C compounds have resulted in deaths.[91,126] There is little to no literature on the long-term effects of 2C use.[126]

Testing and Imaging

No specific testing or imaging is recommended or indicated for phenethylamine ingestion. Laboratory testing and imaging should be directed toward clinical observations and symptoms as needed. 2C phenethylamines are not detected with standard commercial immunoassays.[141] GC/MS or LC-MS/MS can be used to confirm the substance or exposure.[137,141]

Treatment

No specific antidote exists for 2C phenethylamine drugs.[126] Treatment consists of symptom-based goal-directed supportive care with patient education and abstinence from further use. Specific treatment options are discussed in greater detail in the section on management principles.

Summary

2C phenethylamines share the structure of catecholamines, amphetamines, synthetic cathinones, The may be purposefully used or unintentionally encountered as MDMA substitutes. Some 2C drugs show affinity for serotonin receptors, which may impart additional properties in addition to sympathomimetic effects. Specific antidotes are lacking and treatment is primarily supportive.

PIPERAZINES

Piperazine recreational drugs are fully synthetic substances; they do not have natural counterparts. They were initially developed as antihelminthic drugs but later studied as antidepressants.[141] Two main groups of piperazines are used recreationally: benzylpiperazines and phenylpiperazines.[91] Commonly used substances in this class of recreational drugs include 1-benzylpiperazine (BZP), 1-methyl-4-benzylpiperazine, 1-(3-trifluoromethylphenyl)piperazine (TFMPP), 1-(3-chlorophenyl)piperazine, and 1-(2-methoxy-phenyl)piperazine.[30] Piperazines may be found as constituents or substitutes in pills sold as ecstasy or amphetamine.[91,142] Piperazines can be sold in pill or powder form. They may also be obtained as mixtures of piperazine (such as BZP/TFMPP) or in combination with other drugs of abuse.[142] A UK survey demonstrated that piperazines are some of the most common active substances found in drugs purchased on the Internet.[143] Typical users are young males.[144,145]

BZPs enhance neurotransmitter release and reuptake inhibition of dopamine, serotonin, and norepinephrine. In contrast, phenylpiperazines (eg, TFMPP) act directly at serotonin receptors, at serotonin reuptake transporters, and at the serotonin transporter to enhance release of serotonin, but have variable to little effects on dopamine or norepinephrine.[99,146,147] BZP doses typically range from 50 to 250 mg, with effects lasting 6 to 8 hours.[30,141] Dosing, time to onset of symptoms, and duration of effect are variable among piperazines. BZP is not extensively metabolized and is typically excreted unchanged, but may undergo hydroxylation via CYP450 enzymes with methylation by catechol-*O*-methyltransferase and glucuronidation or sulfation.[148] By comparison, TFMPP undergoes extensive hepatic metabolism and is mainly excreted as metabolites. It primarily undergoes hydroxylation, particularly by CYP 2D6 but also 1A2 and 3A4, followed by glucuronidation or sulfation, and partial N-acetylation.[148]

BZP produces psychomotor stimulant effects in humans similar to dexamphetamine.[149] The combination of BZP/TFMPP mimics the actions of MDMA.[150] Overall, most symptoms with piperazine use resemble a sympathomimetic toxidrome.[141,151] Toxicity is difficult to predict on an individual basis despite taking recommended doses.[141] Commonly experienced symptoms include insomnia, anxiety, headaches, nausea, tremors, shakiness, diaphoresis, dizziness, palpitations, shortness of breath, confusion, hallucinations, and paranoia.[145,148,152] Other potential serious effects include seizures, QT interval prolongation, and hyponatremia.[145,153] Because of the serotonergic effects of piperazines, serotonin syndrome is a risk, especially if combined with other serotonergic agents.[141,151] Additional life-threatening complications of BZP use include status epilepticus, hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, and renal failure.[141,148,151] BZP fatalities have been reported and piperazines have been detected in postmortem samples.[154,155] The long-term effects of piperazine are unknown.[141]

No commercial immunoassays are presently available for piperazine detection, but piperazine use may result in a false-positive test for amphetamines.[148,151] Routine qualitative urinary drug screens may be negative. Confirmation of exposure to piperazines can be done via GC-MS, LC-MS, or thin-layer chromatography (TLC).[141,148,151] These testing methods are time consuming and rarely available to aide in the acute management of patients.

No specific antidote exists for piperazine drugs and treatment consists of symptom-based goal-directed supportive care. There is no information on methods for enhancing elimination of piperazines.[141] Specific treatment options are discussed in greater detail in the section on management principles.

KRATOM

Originating from a tree in southeast Asian (*Mitragyna speciosa* Korth), kratom was traditionally used as early as the late 1800s by manual laborers from Thailand and Malaysia for the purposes of euphoria, stimulation, analgesia, and opium withdrawal.[156] Other beneficial effects of kratom include antipyretic, antihypertensive, antiinflammatory, antidiarrheal, hypoglycemic, procirculatory, and sexual prowess properties.[30] Currently, kratom is readily available for purchase on the Internet and has notoriously gained popularity in its use and abuse.[157]

Kratom is most commonly used for the hallucinogenic effects, but may also be used less commonly for management of opioid withdrawal. Mitragynine is merely 1 of more than 2 dozen alkaloids within the plant, and is believed to be the 1 responsible for the opioidlike effects encountered when higher doses are taken.[158] Lower dosing regimens primarily result in a stimulant effect, but these cocainelike effects are not well described. The drug is frequently smoked or ingested after being brewed into a tea. Like its pharmacologic profile, the time of onset and duration of effect (5 minutes and 1 hour, respectively) are dose dependent. These dual properties would lead to inclusion of kratom within a differential diagnosis for several presentations (eg, sympathomimetic, opioid, opioid withdrawal); however, most writings focus on its use for opioid withdrawal. Thus, the most likely patient in the ED will present with either opioid effects or withdrawal. Because this agent is used for opioid withdrawal, and mitragynine has been described to have a potency greater than 10 times that of morphine, kratom withdrawal is also a possibility. Not only can this be a finding in patients who use kratom for opioid withdrawal relief but also has been reported in patients who use kratom for chronic pain syndromes.[159] Kratom withdrawal is indistinguishable from opioid withdrawal and may exhibit identical symptomatology (yawning, rhinorrhea, diarrhea, and irritability).

Generalized tonic-clonic seizurelike activity has also been reported from kratom use.[160] A report describes a 64-year-old man with chronic abdominal pain using kratom in the form of a tea. He seized 30 minutes after ingestion and required mechanical ventilation. Mitragynine was subsequently detected in his urine. Overall, seizures seem exceedingly rare, and other causes such as cerebral hypoxia might have accounted for his condition.[160] One particular form of kratom, named Krypton, may be associated with more severe toxicity and resulting morbidity or mortality. A Swedish case series detailed 9 fatalities in a 1-year period.[161] It was speculated that *O*-desmethyltramadol (an active tramadol metabolite) was intentionally added for greater opioid potency. The combination effect of adding a pharmaceutical to a herb blend for superior potency is of great concern. Herbal regulations differ significantly from pharmaceuticals, and a dose of an active ingredient is rarely standardized.

Care for patients presenting after kratom use is primarily supportive. Attention to airway control is vital in any patient with mental status or respiratory depression. Reports of naloxone reversing kratomlike opioid effects are absent from the literature. However, standard therapy should be implemented for withdrawal symptoms. In the rare event of seizures, benzodiazepines are the first-line therapy.

SALVIA

Although there are hundreds of species of salvia, *Salvia divinorum* is the most relevant to EPs and is the specific species reviewed. A member of the mint family, salvia is native to Mexico and has historically been used during religious ceremonies.[162] The hallucinogenic properties after smoking, ingesting a tea, or chewing the plant leaves are attributed to salvinorin A. Slang terms used for salvia include magic mint, mystic

sage, and Sally D. Head shops or the Internet are a source of prepackaged crushed leaves.

The hallucinogenic properties of salvia differs from many other hallucinogens. Classically, serotonin receptor agonism is the common pharmacologic mechanism producing hallucinations. This includes lysergic acid diethylamide (LSD) and magic mushrooms (psilocybin). Salvia, however, stimulates kappa opioid receptors and is noted to result in perceptual distortions, pseudohallucinations, and an altered sense of self and environment.[163] Chewing and allowing buccal absorption will result in these effects. Oral ingestion, however, will not permit them due of first-pass metabolism or enzymatic degradation of salvia by multiple cytochrome oxidases (eg, CYP 2D6, 2E1).[164]

Classically, salvia is smoked with deep inhalation with valsalva, similar to smoking marijuana.[163] The effects are rapid in onset (30 seconds to 10 minutes depending on exposure route) and quickly dissipate within 30 minutes.[162,163] This brief and intense experience seems to be exaggerated in younger adults and adolescents, and many report visual distortions of body image, out of body experiences, and hearing colors.[162] Most people who use salvia do not seek treatment at a health care facility. One retrospective poison center study documented 37 intentional exposures to salvia over a 10-year period in California.[165] Among these cases, vital sign abnormalities were present in only 2 patients (hypertension and tachycardia in one and isolated tachycardia in the other). Approximately 50% of cases managed included isolated salvia exposure. The most common symptoms recognized among this group included confusion, disorientation, hallucinations, giddiness or dizziness, and a flushed sensation. Benzodiazepine administration was the most common therapeutic intervention.[165] Another case reported from southern California described a 21-year-old man who had no previous medical history or use of psychoactive medications who presented for acute psychosis and paranoia shortly after smoking salvia.[166] He experienced echolalia, paranoia, flight of ideas, and psychomotor agitation for two full days, and then experienced relapsing negative effects after being weaned from risperidone. This may demonstrate salvia's ability to unmask, precipitate, and exacerbate psychiatric disease in vulnerable users. EPs can be expected to offer supportive measures for those who do present after intoxication and provide appropriate follow-up (ie, addiction and psychiatric services) that may ultimately benefit the patient.

MUSHROOMS

Magic shrooms refer to the class of mushrooms that contain the hallucinogenic chemical psilocybin, which is subsequently metabolized to psilocin. Because these compounds resemble serotonin, the subsequent clinical effects are similar to LSD. In most cases, these mushrooms are ingested and result in hallucinations, illusions, and ataxia within one hour.[167] One case reports a rare alleged intravenous injection of fresh psilocybe juice in a 30-year-old man who was at a party. He subsequently experienced vomiting, myalgias, tachycardia, and hyperpyrexia.[168] EPs manage only a small number of cases of hallucinogenic mushroom use. Those who do present are likely manifesting severe nausea, vomiting, diaphoresis, tachycardia, hyperthermia, and rarely seizures.[169]

Classically, patients presenting to the ED might be from a concert setting where ingested mushrooms leads to a bad trip. Another source could be from a college setting, where recreational use is common. According to one survey of nearly 900 undergraduates from a liberal arts college in upstate New York, college students frequently experimented with hallucinogenic mushrooms.[170] Although less than half responded to the survey, the main factor influencing the decision to try hallucinogenic

mushrooms for the first time was curiosity, and users were more likely to have used other drugs (marijuana, cocaine, ecstasy, opiates, nonprescribed prescription drugs, and other hallucinogens).[170]

The goals of management in the clinical setting are like other hallucinogens. Rigorous supportive care, benzodiazepines, and a safe, quiet environment to protect the patient from behavioral toxicity (eg, inappropriately acting on hallucinations) are likely all that is required. Patients with seizures, vital sign abnormalities, or evidence of ongoing psychosis warrant further workup and observation.

HAWAIIAN BABY WOODROSE (*ARGYREIA NERVOSA*)

Lysergamide (LSA) originating in plants may be abused as a hallucinogen, as it is chemically similar to synthetic lysergamide or LSD. Woodrose (*Argyreia nervosa*) chemically differs from morning glory (*Ipomoea violacea*) in that it is contains a higher percentage of ergoline constituents.[171] The seeds from the woodrose are eaten or consumed from an extract after being soaked in water. A commonly ingested dose is five to 10 seeds, which may yield a dose of 2 to 5 mg of LSA, sufficient to result in hallucinations for a duration of four to six hours.[171] Head shops and Internet distribution account for the largest available market of seeds throughout Europe and the United States.[172]

Characteristic symptoms after use are typical of other hallucinogens, however, the effects may be differentiated from the anticipated LSDlike experience. Although increased insight and positive emotional states (eg, euphoria, happiness, delight, altered perceptions of colors and textures, mood elevations) may occur after exposure; tachycardia, hypertension, nausea, vertigo, mydriasis, anxiety, sedation, and a sense of derealization can be considered negative effects.[171,173,174] In recreational users, feelings of loneliness, depression, and suicidal thoughts have also been reported.[174] One case describes a 29-year-old man who ingested an unknown number of seeds after soaking them in water for 2.5 to three hours and then proceeded to become severely agitated and defenestrate a fourth floor window.[171] This patient reportedly had smoked cannabis with another man who witnessed the traumatic death. It is unclear from the report to what extent the ingestion of woodrose seeds contributed to the suicide.

Treatment of intoxication in the emergency setting consists of addressing abnormal vital signs, sedation for anxiety or deliriousness with benzodiazepines, protection, and potentially merely sensory isolation for mild poisoning. Obtaining a psychiatric history and assessing suicidal risk may also be important in the chronic recreational abuser, and may alter ultimate disposition.

MANAGEMENT PRINCIPLES

Many patients presenting under the influence of a drug or substance abused for recreational purposes have an altered sensorium and are unable to provide a robust history surrounding the ingestion. Ideally, knowing the time, route, and intent of use assists in ultimate disposition. For instance, a delayed presentation with ongoing delirium may warrant a computed tomography scan of the brain to rule out another cause of continuing symptomatology. Understanding the route of ingestion is potentially helpful in determining likely symptom duration. In addition, recognizing the patient's intent (ie, recreational vs suicidal) is vital for the purposes of specialty consultation with psychiatry and/or admission or transfer for mental health care.

Much like treating many emergency patients, the management of the poisoned patient consists of sound common sense and aggressive supportive care. The standard

A, B, C approach is a common framework to use when managing a poisoned patient (Table 4). Airway and breathing management are paramount, and any patient with impaired oxygenation and/or ventilatory drive warrants intubation. Likewise, a common indication for intubation and mechanical ventilation is the absence of protective airway reflexes. Emesis and aspiration can further complicate any obtunded patient's course and can be prevented with anticipatory airway management. Circulatory status can be assessed through evaluation of the patient's vital signs and perfusion status. Intravenous crystalloids are a standard first-line attempt to treat hypotension. Infrequently, this patient population may require pressors to increase perfusion. In addition to pulse and blood pressure, a vital sign of fundamental concern is core temperature. Poisoned patients with a high core temperature are prone to have poor outcomes, including major morbidity (eg, multisystem organ failure) and mortality.[117,175] When managing a toxin-induced hyperthermic patient, excess heat generation coupled with impaired heat dissipation is primarily the cause of the hyperthermia rather than a classic pyrogen-induced fever. Treatment with antipyretics is therefore futile. The goal should be to actively and aggressively cool the patient. Ice immersion, mist and fanning, and pharmacologic interventions such as liberal benzodiazepines are principal approaches. This will likely result in normalization of tachycardia as well.

Benzodiazepines serve many useful functions in the agitated patient. Even with absent complex and poor side effect profile (eg, hypotension, anticholinergic effects, increasing serotonergic tone), benzodiazepines are considered a first-line agent in any delirious, altered, seizing, and/or hyperthermic poisoned patient. The dose can be titrated to produce an effect much like ethanol withdrawal.

Decontamination (D) of this patient population is unlikely to provide much benefit. If presenting in the ED, symptomatology is likely already present. Gastric lavage should not be used routinely in this patient population, and activated charcoal only benefits a patient with a protected airway who presents early after ingestion and before the onset of symptomatology. Enhancing elimination (E), through hemodialysis, sodium bicarbonate infusions, and multiple doses of activated charcoal, of xenobiotics is not routinely used in these patients. Hemodialysis, however, should still be considered for severe acid-base or electrolyte disturbances.

The F in the poisoned patient algorithm, refers to focused therapy. Beyond the use of benzodiazepines, as discussed previously, no specific antidotal treatment is likely to benefit most patients within this particular patient group.

Specific diagnostic tests that are likely beneficial include an ECG, specifically taking note of rhythm and interval abnormalities. Sodium bicarbonate boluses for QRS widening (like a tricyclic antidepressant overdose), electrolyte evaluation (potassium,

Table 4
Poisoned patient algorithm

A	Airway
B	Breathing
C	Circulation
D	Decontamination
E	Enhanced elimination
F	Focused therapy (antidotal therapy)
G, H	Get help (consult regional poison center)

calcium, and magnesium concentrations), and correction for patients with a prolonged QTc is reasonable. Acid-base status, urine pregnancy testing, and renal function testing linked to creatinine phosphokinase are important as well. Aggressive hydration is warranted for any patient demonstrating rhabdomyolysis to prevent kidney injury. In addition to intubated patients, those with abnormal vital signs, renal insufficiency, altered mental status, concerning ECG changes, and hemodynamic instability warrant intensive care disposition. Obtaining a concentration of the specific drug ingested is not helpful. Most assays must be sent out and will not guide treatment in real time. Although obtaining the forensic data may help to explain why a patient presented and the corresponding reasons for their pathophysiology, even timely results are unlikely to change the EPs evaluation, management, and/or disposition of such patients. Likewise, a qualitative urine toxicology screen will not be an adequate diagnostic test to rule in or out the agents discussed within this review.

Getting help (G, H) is useful when dealing with patients with exposure to emerging drugs of abuse. Seeking regional poison center assistance (1-800-222–1222 in the United States), discussion with affiliated staff toxicologists, and/or speaking to experts regarding the patient's presentation and treatment schemata are important steps to promote positive patient outcomes. Speaking to an expert in poisoning and overdose helps to direct care and focus on essentials. In addition to providing treatment advice, poison centers provide an essential public health function through surveillance. Some centers are active at legislative levels to help assist law enforcement with emerging trends.[84] Interfacing with other public health agencies and disseminating health alerts and educational materials to facilities when these newer agents are identified is a core public health function of poison centers.

SUMMARY

Drugs of abuse are ever changing and EPs are at the forefront of recognition of these substances. In the Internet age, substances from around the world are available for individuals to use recreationally. Some of these drugs include SCs, synthetic cathinones, phenethylamines, piperazines, herbal products, prescription drugs, and many other substances. These substances also go by a multitude of common street names. Many of the current emerging drugs of abuse result in psychoactive and sympathomimetic effects with excited delirium. Benzodiazepines remain an effective tool to assist in controlling delirium and combating sympathomimetic excess. Regardless of the drug ingested, the mainstay of management includes symptom-based goal-directed supportive care.

REFERENCES

1. Chary M, Genes N, McKenzie A, et al. Leveraging social networks for toxicovigilance. J Med Toxicol 2013;9:184–91.
2. Deluca P, Davey Z, Corazza O, et al. Identifying emerging trends in recreational drug use; outcomes from the Psychonaut Web Mapping Project. Prog Neuropsychopharmacol Biol Psychiatry 2012;39:221–6.
3. Gibbons S. "Legal highs" – novel and emerging psychoactive drugs: a chemical overview for the toxicologist. Clin Toxicol 2012;50:15–24.
4. Sutter ME, Chenoweth J, Albertson TE. Alternative drugs of abuse. Clin Rev Allergy Immunol 2013. http://dx.doi.org/10.1007/s12016-013-8370-2.
5. Aleksander I. Molly: pure but not so simple. 2013. Available at: http://www.nytimes.com/2013/06/23/fashion/molly-pure-but-not-so-simple.html?pagewanted=1&_r=1&hpw&. Accessed June 24, 2013.

6. Okie S. The flood of opioids: a rising tide of deaths. N Engl J Med 2010;363: 1981–5.
7. Ibanez GE, Levi-Minzi MA, Rigg KK, et al. Diversion of benzodiazepines through healthcare sources. J Psychoactive Drugs 2013;45:48–56.
8. Nelson A, Galon P. Exploring the relationship among ADHD, stimulants, and substance abuse. J Child Adolesc Psychiatr Nurs 2012;25:113–8.
9. Paulozzi LJ, Kilbourn EM, Desai HA. Prescription drug monitoring programs and death rates from drug overdose. Pain Med 2011;12:747–54.
10. Manchikanti L. National drug control policy and prescription drug abuse: facts and fallacies. Pain Physician 2007;10:399–424.
11. Pomeranz JL, Taylor LM, Austin SB. Over-the-counter and out-of-control: legal strategies to protect youths from abusing products for weight control. Am J Public Health 2013;103:220–5.
12. Brennan BP, Kanayama G, Pope HG. Performance-enhancing drugs on the web: a growing public-health issue. Am J Addict 2013;22:158–61.
13. Thevis M, Kuuranne T, Geyer H, et al. Annual banned-substance review: analytical approaches in human sports drug testing. Drug Test Anal 2013; 5:1–19.
14. Nelson ME, Bryant SM, Aks SE. Melanotan II injection resulting in systemic toxicity and rhabdomyolysis. Clin Toxicol 2012;50:1165–8.
15. Ward J, Rhyee S, Plansky J, et al. Methoxetamine: a novel ketamine analog and growing health-care concern. Clin Toxicol 2011;49:874–5.
16. Booth RE. Krokodil and other home-produced drugs for injection: a perspective from Ukraine. Int J Drug Policy 2013;24:277–8.
17. Wolk BJ, Ganetsky M, Babu KM. Toxicity of energy drinks. Curr Opin Pediatr 2012;24:243–51.
18. Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animals and humans. Addiction 1996;91:1586–614.
19. Gunderson EW, Haughey HM, Ait-Daoud N, et al. "Spice" and "K2" herbal highs: a case series and systematic review of the clinical effects and biopsychosocial implications of synthetic cannabinoid use in humans. Am J Addict 2012;21: 320–6.
20. Seely KA, Lapoint J, Moran JH, et al. Spice drugs are more than harmless herbal blends: a review of the pharmacology and toxicology of synthetic cannabinoids. Prog Neuropsychopharmacol Biol Psychiatry 2012;39:234–43.
21. Seely KA, Prather PL, James LP, et al. Marijuana-based drugs: innovative therapeutics or designer drugs of abuse. Mol Interv 2011;11:36–51.
22. Auwärter V, Dresen S, Weinmann W, et al. Spice and other herbal blends: harmless incense or cannabinoid designer drugs? J Mass Spectrom 2009;44:832–7.
23. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). EMCDDA 2009 thematic paper – understanding the 'Spice' phenomenon. Luxembourg: Office for Official Publications of the European Communities; 2009.
24. Vardakou I, Pistos C, Spiliopoulou CH. Spice drugs as a new trend: mode of action, identification and legislation. Toxicol Lett 2010;197:157–62.
25. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Synthetic cannabinoids and 'Spice.' Available at: http://www.emcdda.europa.eu/publications/drug-profiles/synthetic-cannabinoids. Accessed September 2, 2013.
26. Einhorn L, Nagy C, Furnas B, et al. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. J Clin Pharmacol 1981;21:64S–9S.

27. United States Adopted Names Council: Statement on a nonprioprietary name. Available at: http://www.ama-assn.org/ama1/pub/upload/mm/365/nabiximols.pdf. Accessed June 4, 2013.
28. Weissman A, Milne GM, Melvin LS Jr. Cannabimimetic activity from CP-47,497, a derivative of 3-phenylcyclohexanol. J Pharmacol Exp Ther 1982;223:516–23.
29. Bell MR, D'Ambra TE, Kumar V, et al. Antinociceptive (aminoalkyl)indoles. J Med Chem 1991;34:1099–110.
30. Rosenbaum CD, Carreiro SP, Babu KM. Here today, gone tomorrow… and back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones (bath salts), Kratom, Salvia divinorum, methoxetamine, and piperazines. J Med Toxicol 2012;8:15–32.
31. Huffman JW, Dai D. Design, synthesis and pharmacology of cannabimimetic indoles. Bioorg Med Chem Lett 1994;4:563–6.
32. Huffman JW, Yu S, Showalter V, et al. Synthesis and pharmacology of a very potent cannabinoid lacking a phenolic hydroxyl with high affinity for the CB2 receptor. J Med Chem 1996;39:3875–7.
33. Wiley JL, Comptom DR, Dai D, et al. Structure-activity relationships of indole- and pyrrole-derived cannabinoids. J Pharmacol Exp Ther 1998;285:995–1004.
34. Huffman JW. Cannabimimetic indoles, pyrroles, and indenes: structure-activity relationships and receptor interactions. In: Reggio PH, editor. The cannabinoid receptors, 1. New York: Humana Press; 2009. p. 49–94.
35. Atwood BK, Huffman J, Straiker A, et al. JWH018, a common constituent of 'Spice' herbal blends, is a potent and efficacious cannabinoid CB_1 receptor agonist. Br J Pharmacol 2010;160:585–93.
36. Lapoint J, James LP, Moran CL, et al. Severe toxicity following synthetic cannabinoid ingestion. Clin Toxicol 2011;49:760–4.
37. Wood KE. Exposure to bath salts and synthetic tetrahydrocannabinol from 2009 to 2012 in the United States. J Pediatr 2013;163:213–6.
38. Schedules of controlled substances: temporary placement of five synthetic cannabinoids into schedule I [FR Doc No: 11075–11078]. Drug Enforcement Administration (DEA). Available at: http://www.deadiversion.usdoj.gov/fed_regs/rules/2011/fr0301.htm. Accessed June 5, 2013.
39. Moran CL, Le VH, Chimalakonda KC, et al. Quantitative measurement of JWH-018 and JWH-073 metabolites excreted in human urine. Anal Chem 2011;83:4228–36.
40. Johnston LD, O'Malley PM, Bachman JG, et al. Monitoring the future national results on drug use: 2012 overview, key findings on adolescent drug use. Ann Arbor (MI): Institute for Social Research, The University of Michigan; 2013. Available at: http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2012.pdf. Accessed June 6, 2013.
41. Heltsley R, Shelby MK, Crouch DJ, et al. Prevalence of synthetic cannabinoids in U.S. athletes: initial findings. J Anal Toxicol 2012;36:588–93.
42. Hoyte CO, Jacob J, Monte AA, et al. A characterization of synthetic cannabinoid exposures reported to the national poison data system in 2010. Ann Emerg Med 2012;60:435–8.
43. Forrester MB, Kleinschmidt K, Schwarz E, et al. Synthetic cannabinoid and marijuana exposures reported to poison centers. Hum Exp Toxicol 2012;31:1006–11.
44. Winstock AR, Barratt MJ. Synthetic cannabis: a comparison of patterns of use and effect profile with natural cannabis in a large global sample. Drug Alcohol Depend 2013;131:106–11.

45. Lank PM, Pines E, Mycyk MB. Emergency physicians' knowledge of cannabinoid designer drugs. West J Emerg Med 2013;14(5):1–4. Available at: http://www.escholarship.org/uc/item/9mk2951f. Accessed September 2, 2013.
46. Ameri A. The effects of cannabinoids on the brain. Prog Neurobiol 1999;58:315–48.
47. Pertwee RG. Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. Curr Med Chem 2010;17:1360–81.
48. Gronewold A, Skopp G. A preliminary investigation on the distribution of cannabinoids in man. Forensic Sci Int 2011;210:e7–11.
49. Shim JY, Welsh WJ, Howlett AC. Homology model of the CB1 cannabinoid receptor: sites critical for nonclassical cannabinoid agonist interaction. Biopolymers 2003;71:169–89.
50. Teske J, Weller JP, Fieguth A, et al. Sensitive and rapid quantification of the cannabinoid receptor agonist naphthalen-1-yl-(1-pentylindol-3-yl) methanone (JWH-018) in human serum by liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 2010;878:2659–63.
51. Brents LK, Reichard EE, Zimmerman SM, et al. Phase I hydroxylated metabolites of the K2 synthetic cannabinoid JWH-018 retain in vitro and in vivo cannabinoid 1 receptor affinity and activity. PLoS One 2011;6:e21917.
52. Rajasekaran M, Brents LK, Franks LN, et al. Human metabolites of synthetic cannabinoids JWH-018 and JWH-073 bind with high affinity and act as potent agonists at cannabinoid type-2 receptors. Toxicol Appl Pharmacol 2013;269:100–8.
53. Castellanos D, Singh S, Thornton G, et al. Synthetic cannabinoid use: a case series of adolescents. J Adolesc Health 2011;49:347–9.
54. Hurst D, Loeffler G, McLay R. Psychosis associated with synthetic cannabinoid agonists: a case series. Am J Psychiatry 2011;168:1119.
55. Müller H, Sperling W, Köhrmann M, et al. The synthetic cannabinoid Spice as a trigger for an acute exacerbation of cannabis induced recurrent psychotic episodes. Schizophr Res 2010;118:309–10.
56. Every-Palmer S. Synthetic cannabinoid JWH-018 and psychosis: an explorative study. Drug Alcohol Depend 2011;117:152–7.
57. Schneir AB, Cullen J, Ly BT. "Spice" girls: synthetic cannabinoid intoxication. J Emerg Med 2011;40:296–9.
58. Schneir AB, Baumbacher T. Convulsions associated with the use of a synthetic cannabinoid product. J Med Toxicol 2012;8:62–4.
59. Tofighi B, Lee JD. Internet highs – seizures after consumption of synthetic cannabinoids purchased online. J Addict Med 2012;6:240–1.
60. Pant S, Deshmukh A, Dholaria B, et al. Spicy seizure. Am J Med Sci 2012;344:67–8.
61. Mir A, Obafemi A, Young A, et al. Myocardial infarction associated with use of the synthetic cannabinoid K2. Pediatrics 2011;128(6):e1622–7.
62. Simmons JR, Skinner CG, Williams J, et al. Intoxication from smoking "Spice". Ann Emerg Med 2011;57(2):187–8.
63. Centers for Disease Control and Prevention (CDC). Acute kidney injury associated with synthetic cannabinoid use – multiple states 2012. MMWR Morb Mortal Wkly Rep 2012;62:93–8.
64. Alhadi S, Tiwari A, Vohra R, et al. High times, low sats: diffuse pulmonary infiltrates associated with chronic synthetic cannabinoid use. J Med Toxicol 2013;9:199–206.

65. Fattore L, Fratta W. Beyond THC: the new generation of cannabinoid designer drugs. Front Behav Neurosci 2011;5:1–12.
66. Bronstein AC, Spyker DA, Cantilena LR, et al. 2011 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th annual report. Clin Toxicol 2012;50:911–1164.
67. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A 2012; 109:E2657–64.
68. Duffy A, Milin R. Case study: withdrawal syndrome in adolescent chronic cannabis users. J Am Acad Child Adolesc Psychiatry 1996;35:1618–21.
69. Haney M. The marijuana withdrawal syndrome: diagnosis and treatment. Curr Psychiatry Rep 2005;7:360–6.
70. Nacca N, Vatti D, Sullivan R, et al. The synthetic cannabinoid withdrawal syndrome. J Addict Med 2013;7:296–8.
71. Zimmermann US, Winkelmann PR, Pilhatsch M, et al. Withdrawal phenomena and dependence syndrome after the consumption of "Spice Gold". Dtsch Arztebl Int 2009;106:464–7.
72. National Medical Services (NMS) labs. NMS Labs Online Test Catalog. 2013. Available at: http://www.nmslabs.com/test-catalog/synthetic%20cannabinoids@0. Accessed June 10, 2013.
73. World Health Organization Expert Committee on Drug Dependence. Assessment of khat (*Catha edulis* Forsk). 34th ECDD. Geneva (Switzerland): WHO Expert Committee on Drug Dependence; 2006. Available at: http://www.who.int/medicines/areas/quality_safety/4.4KhatCritReview.pdf. Accessed June 11, 2013.
74. Prosser JM, Nelson LS. The toxicology of bath salts: a review of synthetic cathinones. J Med Toxicol 2012;8:33–42.
75. Brenneisen R, Fisch HU, Koelbing U, et al. Amphetamine-like effects in humans of the khat alkaloid cathinone. Br J Clin Pharmacol 1990;30:825–8.
76. Ali WM, Zubaid M, Al-Motarreb A, et al. Association of khat chewing with increased risk of stroke and death in patients presents with acute coronary syndrome. Mayo Clin Proc 2010;85:974–80.
77. Hyde JF, Browning E, Adams R. Synthetic homologs of D,L-ephedrine. J Am Chem Soc 1928;50:2287–92.
78. Emerson TS, Cisek JE. Methcathinone: a Russian designer amphetamine infiltrates the rural Midwest. Ann Emerg Med 1993;22:1897–903.
79. Mehta MB. United States patent 3,819,706: Meta-chloro substituted α-butylaminopropiophenones. United States Patent and Trademark Office (USPTO). 1974. Available at: http://patimg1.uspto.gov/.piw?Docid=03819706&homeurl=http%3A%2F%2Fpatft.uspto.gov%2Fnetacgi%2Fnph-Parser%3FSect1%3DPTO1%2526Sect2%3DHITOFF%2526d%3DPALL%2526p%3D1%2526u%3D%25252Fnetahtml%25252FPTO%25252Fsrchnum.htm%2526r%3D1%2526f%3DG%2526l%3D50%2526s1%3D3819706.PN.%2526OS%3DPN%2F3819706%2526RS%3DPN%2F3819706&PageNum=&Rtype=&SectionNum=&idkey=NONE&Input=View+first+page. Accessed June 13, 2013.
80. United States Drug Enforcement Administration. Methcathinone. 2013. Available at: http://www.justice.gov/dea_old/concern/methcathinone.html. Accessed June 13, 2013.
81. Psychonaut Web Mapping Research Group. Mephedrone. London: Institute of Psychiatry, King's College London; 2009. Available at: http://www.psychonautproject.eu/newsletters/n2.php. Accessed June 13, 2013.

82. Dargan PI, Albert S, Wood DM. Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. QJM 2010;103:875–9.
83. Winstock AR, Mitcheson LR, Deluca P, et al. Mephedrone, new kid for the chop? Addiction 2010;106:154–61.
84. Warrick BJ, Hill M, Hekman K, et al. A 9-state analysis of designer stimulant, "bath salt, " hospital visits reported to poison control centers. Ann Emerg Med 2013;62:244–51.
85. American Association of Poison Control Centers. Bath salts data. 2013. Available at: https://aapcc.s3.amazonaws.com/files/library/Bath_Salts_Data_for_Website_5.31.2013.pdf. Accessed June 14, 2013.
86. American Association of Poison Control Centers. Synthetic marijuana data. 2013. Available at: https://aapcc.s3.amazonaws.com/files/library/Synthetic_Marijuana_Data_for_Website_5.31.2013.pdf. Accessed June 14, 2013.
87. Winstock A, Mitcheson L, Marsden J. Mephedrone: still available and twice the price. Lancet 2010;376:1537.
88. Gibbons S, Zloh M. An analysis of the 'legal high' mephedrone. Bioorg Med Chem Lett 2010;20:4135–9.
89. US Department of Justice DEA. Notice of intent – scheduled of controlled substances: temporary placement of three synthetic cathinones into schedule I. Microgram Bulletin 2011;44:57–65.
90. 112th Congress. S. 3190: Synthetic Drug Abuse Prevention Act of 2012. Sec 2. Addition of Synthetic Drugs to Schedule I of the Controlled Substances Act. Washington, DC: Library of Congress [May 16, 2012]. Available at: http://www.govtrack.us/congress/bills/112/s3190/text. Accessed July 2, 2013.
91. Hill SL, Thomas SH. Clinical toxicology of newer recreational drugs. Clin Toxicol 2011;49:705–19.
92. Marinetti LJ, Antonides HM. Analysis of synthetic cathinones commonly found in bath salts in human performance and postmortem toxicology: method development, drug distribution and interpretation of results. J Anal Toxicol 2013;37:135–46.
93. James D, Adams RD, Spears R, et al. Clinical characteristics of mephedrone toxicity reported to the UK National Poisons Information Service. Emerg Med J 2011;28:686–9.
94. Schifano F, Albanese A, Fergus S, et al. Mephedrone (4-methylmethcathinone; 'meow-meow'): chemical, pharmacological and clinical issues. Psychopharmacology 2011;214:593–602.
95. Wood DM, Davies S, Greene SL, et al. Case series of individuals with analytically confirmed acute mephedrone toxicity. Clin Toxicol 2010;48:924–7.
96. Coppola M, Mondola R. Synthetic cathinones: chemistry, pharmacology, and toxicology of a new class of designer drugs of abuse marketed as "bath salts" or "plant food". Toxicol Lett 2012;211:144–9.
97. Cameron K, Kolanos R, Vekariya R, et al. Mephedrone and methylenedioxypyrovalerone (MDPV), major constituents of "bath salts, " produce opposite effects at the human dopamine transporter. Psychopharmacology 2013;227:493–9.
98. Cozzi NV, Sievert MK, Shulgin AT, et al. Inhibition of plasma membrane monoamine transporters by β-ketoamphetamines. Eur J Pharmacol 1999;381:63–9.
99. Nagai F, Nonaka R, Satoh Hasashi Kamimura K. The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. Eur J Pharmacol 2007;559:132–7.

100. Meyer MR, Wilhelm J, Peters FT, et al. Beta-ketoamphetamines: studies on the metabolism of the designer drug mephedrone and toxicological detection of mephedrone, butylone, and methylone in urine using gas chromatography-mass spectrometry. Anal Bioanal Chem 2010;397:1225–33.
101. Zaitsu K, Katagi M, Tatsuno M, et al. Recently abused β-keto derivatives of 3,4-methylenedioxyphenylalkylamines: a review of the metabolisms and toxicological analysis. Forensic Toxicol 2011;29:73–84.
102. Meyer MR, Du P, Schuster F, et al. Studies on the metabolism of the α-pyrrolidinophenone designer drug methylenedioxy-pyrovalerone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high resolution MS and its detectability in urine by GC-MS. J Mass Spectrom 2010;45:1426–42.
103. Wood DM, Davies S, Puchnarewicz M, et al. Recreational use of mephedrone (4-methylmethcathinone, 4-MMC) with associated sympathomimetic toxicity. J Med Toxicol 2010;6:327–30.
104. Murphy CM, Dulaney AR, Beuhler MC, et al. "Bath Salts" and "Plant Food" products: the experience of one regional US Poison Center. J Med Toxicol 2013;9:42–8.
105. Nicholson PJ, Quinn MJ, Dodd JD. Headshop heartache: acute mephedone 'meow' myocarditis. Heart 2010;96:2051–2.
106. Wyman JF, Lavins ES, Engelhart D, et al. Postmortem tissue distribution of MDPV following lethal intoxication by "Bath Salts". J Anal Toxicol 2013;37:182–5.
107. Penders TM, Gestring RE, Vilensky DA. Excited delirium following the use of synthetic cathinones (bath salts). Gen Hosp Psychiatry 2012;34:647–50.
108. Thornton SL, Gerona RR, Tomaszewksi CA. Psychosis from a bath salt product containing flephedrone and MDPV with serum, urine, and product quantification. J Med Toxicol 2012;8:310–3.
109. Stoica MV, Felthous AR. Acute psychosis induced by bath salts: a case report with clinical and forensic implications. J Forensic Sci 2013;58:530–3.
110. Murray BL, Murphy CM, Beuhler MC. Death following recreational use of designer drug "Bath Salts" containing 3,4-methylenedioxypyrovalerone (MDPV). J Med Toxicol 2012;8:69–75.
111. Olives TD, Orozco BS, Stellpflug SJ. Bath salts: the ivory wave of trouble. West J Emerg Med 2012;13:58–62.
112. Boulanger-Gobeil C, St-Onge M, Laliberté M, et al. Seizures and hyponatremia related to ethcathinone and methylone poisoning. J Med Toxicol 2012;8:59–61.
113. Winstock A, Mitcheson L, Ramsey J, et al. Mephedrone: use, subjective effects and health risk. Addiction 2011;106:1991–6.
114. Warrick BJ, Wilson J, Hedge M, et al. Lethal serotonin syndrome after methylone and butylone ingestion. J Med Toxicol 2012;8:65–8.
115. Levine M, Levitan R, Skolnik A. Compartment syndrome after "Bath Salts" use: a case series. Ann Emerg Med 2012;61:480–3.
116. Borek HA, Holstege CP. Hyperthermia and multiorgan failure after abuse of "Bath Salts" containing 3,4-methylenedioxypyrovalerone. Ann Emerg Med 2012;60:103–5.
117. Rosenberg J, Pentel P, Pond S, et al. Hyperthermia associated with drug intoxication. Crit Care Med 1986;14:964–9.
118. Torrance H, Cooper G. The detection of mephedrone (4-methylmethcathinone) in 4 fatalities in Scotland. Forensic Sci Int 2010;202:e62–3.
119. Carbone PN, Carbone DL, Carstairs SD, et al. Sudden cardiac death associated with methylone use. Am J Forensic Med Pathol 2013;34:26–8.

120. Maskell PD, De Paoli G, Seneviratne C, et al. Mephedrone (4-methylmethcathinone)-related deaths. J Anal Toxicol 2011;35:188–91.
121. Sparago M, Wlos J, Yaun J, et al. Neurotoxic and pharmacologic studies on enantiomers of the N-methylated analog of cathinone (methcathinone): a new drug of abuse. J Pharmacol Exp Ther 1996;279:1043–52.
122. McCann UD, Wong DF, Yokoi F, et al. Reduced striatal dopamine transporter density in the abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [11C]WIN-35,428. J Neurosci 1998;18:8417–22.
123. Petrie M, Lynch KL, Ekins S, et al. Cross-reactivity studies and predictive modeling of "Bath Salts" and other amphetamine-type stimulants with amphetamine screening immunoassays. Clin Toxicol 2013;51:83–91.
124. Swortwood MJ, Boland DM, DeCaprio AP. Determination of 32 cathinone derivatives and other designer drugs in serum by comprehensive LC-QQQ-MS/MS analysis. Anal Bioanal Chem 2013;405:1383–97.
125. National Medical Services (NMS) labs. NMS Labs Online Test Catalog. 2013. Available at: http://www.nmslabs.com/test-catalog/bath%20salts@0. Accessed June 18, 2013.
126. Dean BV, Stellpflug SL, Burnett AM, et al. 2C or Not 2C: phenethylamine designer drug review. J Med Toxicol 2013;9:172–8.
127. Shulgin AT, Shulgin A. PiHKAL - a chemical love story. Berkley (CA): Transform Press; 1991.
128. Benzenhöfer U, Passie T. Rediscovering MDMA (ecstasy): the role of the American chemist Alexander T. Shulgin. Addiction 2010;105:1355–61.
129. Caudevilla-Gálligo F, Riba J, Ventura M, et al. 4-Bromo-2,5-dimethoxyphenethylamine (2C-B): presence in the recreational drug market in Spain, pattern of use and subjective effects. J Psychopharmacol 2012;26:1026–35.
130. de Boer D, Bosman I. A new trend in drugs-of-abuse; the 2C series of phenethylamine designer drugs. Pharm World Sci 2004;26:110–3.
131. Giroud C, Augsburger M, Rivier L, et al. 2C-B: a new psychoactive phenethylamine recently discovered in Ecstasy tablets sold on the Swiss black market. J Anal Toxicol 1998;22:345–54.
132. Sanders B, Lankenau SE, Bloom JJ, et al. "Research Chemicals": tryptamine and phenethylamine use among high-risk youth. Subst Use Misuse 2008;43:389–402.
133. Topeff JM, Ellsworth H, Willhite LA, et al. A case series of symptomatic patients, including one fatality, following 2C-E exposure. Clin Toxicol 2011;49:526.
134. Maurer HH. Chemistry, pharmacology, and metabolism of emerging drugs of abuse. Ther Drug Monit 2010;32:544–9.
135. Saez P, Borges Y, Gonzalez E, et al. Alpha-adrenergic and 5-HT2-serotonergic effects of some beta-phenylethylamines on isolated rat thoracic aorta. Gen Pharmacol 1994;25:211–6.
136. Carmo H, Hengstler JG, de Boer D, et al. Metabolic pathways of 4-bromo-2,5-dimethoxyphenethylamine (2C-B): analysis of phase I metabolism with hepatocytes of six species including human. Toxicology 2005;206:75–89.
137. Theobald DS, Maurer HH. Studies on the metabolism and toxicological detection of the designer drug 2,5-dimethoxy-4-methyl-β-phenethylamine (2C-D) in rat urine using gas chromatographic/mass spectrometric techniques. J Mass Spectrom 2006;41:1509–19.

138. Theobald DS, Maurer HH. Identification of monoamine oxidase and cytochrome P450 isoenzymes involved in the deamination of phenethylamine-derived designer drugs (2C-series). Biochem Pharmacol 2007;73:287–97.
139. Ambrose JB, Bennett HD, Lee HS, et al. Cerebral vasculopathy after 4-bromo-2,5-dimethoxyphenethylamine ingestion. Neurologist 2010;16:199–202.
140. Bosak A, LoVecchio F, Levine M. Recurrent seizures and serotonin syndrome following "2C-I" ingestion. J Med Toxicol 2013;9:196–8.
141. Schep LJ, Slaughter RJ, Vale JA, et al. The clinical toxicology of the designer "party pills" benzylpiperazine and trifluoromethylphenylpiperazine. Clin Toxicol 2011;49:131–41.
142. Staack RF. Piperazine designer drugs of abuse. Lancet 2007;369:1411–3.
143. Davies S, Wood DM, Smith G, et al. Purchasing 'legal highs' on the Internet – is there consistency in what you get? QJM 2010;103:489–93.
144. Wilkins C, Sweetsur P, Girling M. Patterns of benzylpiperazine/trifluoromethylphenylpiperazine party pill use and adverse effects in a population sample in New Zealand. Drug Alcohol Rev 2008;27:633–9.
145. Gee P, Gilbert M, Richardson S. Toxicity from the recreational use of 1-benzylpiperazine. Clin Toxicol 2008;46:802–7.
146. Baumann MH, Clark RD, Budzynski AG, et al. Effects of "Legal X" piperazine analogs on dopamine and serotonin release in rat brain. Ann N Y Acad Sci 2004;1025:189–97.
147. Baumann MH, Clark RD, Budzynski AG, et al. N-substituted piperazines abused by humans mimic the molecular mechanism of 3,4-methylenedioxymethamphetamine (MDMA, or 'Ecstasy'). Neuropsychopharmacology 2005;30:550–60.
148. Arbo MD, Bastos ML, Carmo HF. Piperazine compounds as drugs of abuse. Drug Alcohol Depend 2012;122:174–85.
149. Bye C, Munro-Faure AD, Peck AW, et al. A comparison of the effects of 1-benzylpiperazine and dexamphetamine on human performance tests. Eur J Clin Pharmacol 1973;6:163–9.
150. de Boer D, Bosman IJ, Hidvégi E, et al. Piperazine-like compounds: a new group of designer drugs-of-abuse on the European market. Forensic Sci Int 2001;121:47–56.
151. Gee P, Jerram T, Bowie D. Multiorgan failure from 1-benyzlpiperazine ingestion – legal high or lethal high? Clin Toxicol 2010;48:230–3.
152. Wilkins C, Sweetsur P. Differences in harm from legal BZP/TFMPP party pills between North Island and South Island users in New Zealand: a case of effective industry self-regulation? Int J Drug Policy 2010;21:86–90.
153. Wood DM, Dargan PI, Button J, et al. Collapse, reported seizure – and an unexpected pill. Lancet 2007;369:1490.
154. Balmelli C, Kupferschmidt H, Rentsch K, et al. Fatal brain edema after ingestion of ecstasy and benzylpiperazine. Dtsch Med Wochenschr 2001;126:809–11.
155. Elliott S, Smith C. Investigation of the first deaths in the United Kingdom involving the detection and quantification of the piperazines BZP and 3-TFMPP. J Anal Toxicol 2008;32:172–7.
156. Shellard EJ. Ethnopharmacology of Kratom and the mitragyna alkaloids. J Ethnopharmacol 1989;25:123–4.
157. Boyer EW, Babu KM, Macalino GE, et al. Self-treatment of opioid withdrawal with a dietary supplement, Kratom. Am J Addict 2007;16:352–6.
158. Thongpradichote S, Matsumoto K, Tohda M, et al. Identification of opioid receptor subtypes in antinociceptive actions of supraspinally-administered mitragynine in mice. Life Sci 1998;62:1371–8.

159. Suwanlert S. A study of Kratom eaters in Thailand. Bull Narc 1975;27:21–7.
160. Nelson JL, Lapoint J, Hodgman MJ, et al. Seizures and coma following Kratom (*Mitragynina speciosa* Korth) exposure. J Med Toxicol 2010;6:424–6.
161. Kronstrand R, Roman M, Thelander G, et al. Unintentional fatal intoxications with mitragynine and O-desmethyltramadol from the herbal blend Krypton. J Anal Toxicol 2011;35:242–7.
162. Kelly BC. Legally tripping: a qualitative profile of *Salvia divinorum* use among young adults. J Psychoactive Drugs 2011;43:46–54.
163. Baggott MJ, Erowid E, Erowid F, et al. Use patterns and self-reported effects of *Salvia divinorum*: an internet-based survey. Drug Alcohol Depend 2010;111: 250–6.
164. Tsujikawa K, Kuwayama K, Miyaguchi H, et al. In vitro stability and metabolism of Salvinorin A in rat plasma. Xenobiotica 2009;39:391–8.
165. Rais V, Seefeld A, Cantrell L, et al. *Salvia divinorum*: exposures reported to a statewide poison control system over 10 years. J Emerg Med 2011;40:643–50.
166. Przekop P, Lee T. Persistent psychosis associated with *Salvia divinorum* use. Am J Psychiatry 2009;166:832.
167. Hatfield GM, Brady LR. Toxins of higher fungi. Lloydia 1975;38:36–55.
168. Curry SC, Rose MC. Intravenous mushroom poisoning. Ann Emerg Med 1985; 14:900–2.
169. McClintock RL, Watts DJ, Melanson S. Unrecognized magic mushroom abuse in a 28-year-old man. Am J Emerg Med 2008;26:972.e3–4.
170. Hallock RM, Dean A, Knecht ZA, et al. A survey of hallucinogenic mushroom use, factors related to usage, and perceptions of use among college students. Drug Alcohol Depend 2013;130:245–8.
171. Klinke HB, Muller IB, Steffenrud S, et al. Two cases of lysergamide intoxication by ingestion of seeds from Hawaiian baby woodrose. Forensic Sci Int 2010;197: e1–5.
172. Schmidt MM, Sharma A, Schifano F, et al. "Legal highs" on the net: evaluation of UK-based websites, products and product information. Forensic Sci Int 2011; 206:92–7.
173. Kremer C, Paulke A, Wunder C, et al. Variable adverse effects in subjects after ingestion of equal doses of *Argyreia nervosa* seeds. Forensic Sci Int 2012;214: e6–8.
174. Juszczak GR, Swiergiel AH. Recreational use of D-lysergamide from the seeds of *Argyreia nervosa*, *Ipomoea tricolor*, *Ipomoea violacea*, and *Ipomoea purpurea* in Poland. J Psychoactive Drugs 2013;45:79–93.
175. Rusyniak DE, Sprague JE. Toxin-induced hyperthermic syndromes. Med Clin North Am 2005;89:1277–96.