The past decade has seen the emergence of new drugs of abuse in the United States. Most of these are variations of well-known illicit stimulants, hallucinogens, and depressants,\(^1\) some are the products of drug mechanisms engineered for therapeutic benefit, and others have become available to U.S. consumers because of globalization.

Two of the drugs routinely seen by the U.S. medical community are synthetic cannabinoids, which are found in "spice" drugs, and synthetic cathinones.

Figure 1. Retrograde signaling by endocannabinoids. The endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG) are synthesized in postsynaptic target cells such as hippocampal pyramidal cells (right). Synthesis is initiated by calcium influx through voltage-gated calcium channels, or by the activation of G protein-coupled neurotransmitter receptors, including type I metabotropic glutamate receptors (mGluR) or muscarinic acetylcholine receptors (mAChR). The endocannabinoids gain access to the extracellular space and activate cannabinoid receptors (CB1R) found concentrated on certain nerve terminals (eg, cholecystokinin-containing GABAergic interneurons in hippocampus). CB1 activation causes presynaptic inhibition of gamma-aminobutyric acid (GABA) or glutamate release by inhibiting calcium channels, interfering with vesicle release, and activating potassium channels. The endocannabinoids are taken up into postsynaptic or presynaptic cells by the anandamide transporter (AT). The degradative enzyme fatty acid amide hydrolase (FAAH) is present in postsynaptic cells, and monoglyceride lipase (not shown), which degrades 2-AG, is found in presynaptic terminals. (From the article “Endocannabinoids: Getting the Message Across" by Bradley Alger. Proceedings of the National Academy of Sciences. 2004;101:23 [doi:10.1073/pnas.0402935101; http://www.pnas.org/content/101/23/8512]; Copyright © 2004, The National Academy of Sciences; with permission.)
these drugs, it is now possible to characterize intoxication syndromes. There is limited peer-reviewed guidance on signs and symptoms of synthetic cannabinoid and cathinone abuse. Clinical diagnosis of spice and bath salt intoxication is important because standard screening tests do not detect the drugs in blood and urine.

This article reviews the literature on these new drugs of abuse to help demystify the evaluation of a patient with a suspected ingestion. It focuses on synthetic cannabinoids and cathinones, following with a shorter discussion of other emerging drugs.

CASE

A 27-year-old man without a known psychiatric history was brought to a local emergency department (ED) for evaluation after exhibiting bizarre behavior. Earlier on the day of the evaluation, he disembarked from a ship by climbing down a mooring line while clasping a knife in his teeth. Witnesses said he ran down the pier without incident. His whereabouts for the next several hours were unknown. However, just prior to his arrest he was found naked in a local yacht club brandishing the knife and yelling almost incoherently about “the end of the world.” After several days of inpatient psychiatric hospitalization, he outlined a somewhat coherent story of the events that led to his hospitalization. The history provided by the patient and witnesses, along with a positive urine drug screen for synthetic cannabinoids, highlights the dangers of this substance.

SYNTHETIC CANNABINOIDS

Background

Synthetic cannabinoids are the main active ingredient in “spice” and related products. The term “spice” refers to the mixture of plant materials and additives that are thought to serve as a vehicle/masking agent for artificial psychoactive cannabinoids. Herbal marijuana alternatives have been available since the early 2000s, initially in Europe. Identified by authorities in 2008, synthetic cannabinoid additives are a group of diverse chemicals with the property of agonism at the cannabinoid1 (CB1) cell receptor, the site of action of Δ9-tetrahydrocannabinol (THC) and endogenous cannabinoids. Commercial laboratories such as Pfizer developed these chemicals through research into the therapeutic properties of marijuana, and they have been released by labs in clusters of related compounds since the 1960s.1 Spice use has been seen in the United States since 2008. Its use has escalated in the past 3 years, and it now has a place on the Substance Abuse and Mental Health Services Administration (SAMHSA) Drug Abuse Warning Network (DAWN) Report among the most common drugs of abuse. According to the report, usage grew from an unreportable level in 2009 to 3.7 ED visits per 100,000 in 2010 and to 9.2 visits per 100,000 in 2011.2 Simultaneously, the number of calls to poison control centers for spice increased from 2,906 in 2010 to 6,959 in 2011 according to the American Association of Poison Control Centers.2

Drug laws originally did not control synthetic cannabinoids, which were legally obtainable from head shops and gas stations.3 The Office of National Drug Control Policy and Department of Justice created laws against them2,4 but they do not fully regulate usage because new cannabinoid derivatives are constantly replacing banned chemicals in spice.

Basic Science

As mentioned previously, synthetic cannabinoids exert their pharmacologic effect at the CB1 receptor. CB1 and CB2 receptors interact with synthetic cannabinoids, THC, and the endogenous ligands such as anandamide.1 Anandamide appears to play a role in modulating neurotransmission, such as by inhibiting synaptic impulses in the hippocampus and protecting against glutamnergic excitotoxicity5 (Figure 1). Whereas CB2 receptors have a relative distribution in the peripheral tissue and are associated with white blood cells, CB1 is mostly localized to the central nervous system, including the hypothalamus and limbic system, and is the mediator of cannabinoid drug signs and symptoms. There are seven different structural categories of synthetic cannabinoids and many variants within groups. A compound called JWH-081 from the JWH series is thought to be most prevalent.6 Other prevalent compound series include the HU and CP series. Despite their differences, the diverse drugs are similar in that they generally have 20 to 26 carbons and are lipid-soluble and volatile. They demonstrate a greater affinity and, therefore, more potent interaction with the CB1 receptor than THC.6 For example, HU-210 is 100 to 800 times more potent than THC.7 They are also full agonists, whereas marijuana is a partial agonist.8 Typical doses may be less than 1 mg.6

Similarities to Marijuana

As engineered mimickers of THC at the CB1 receptor, synthetic cannabinoids induce pharmacologic effects similar to those of marijuana (Table 1). The similarity is of prime importance in understanding and recognizing the symptoms of spice intoxication. Marijuana intoxication overlaps with synthetic cannabinoid intoxication in the subjective psychological and somatic experiences as well as the clinical signs. Therefore, these drugs induce relaxation; euphoria; perceptual

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Disturbances such as hallucinations and an altered sense of time; intensified sensory experiences; cognitive impairment including amnestic symptoms; and increased reaction time. They may also cause xerostomia, injected conjunctivae, tachycardia, and tachycardia—consistent with marijuana intoxication.

### Differences from Marijuana

A number of synthetic cannabinoid features have emerged as distinct from the symptoms of marijuana abuse. Some or all of these effects could be attributable to the full agonism at the CB1 receptor. One salient finding is the psychological effect of spice, especially the prominent agitation, if not frank psychosis. Patients can experience paranoid delusions and command-type hallucinations as seen after marijuana abuse, but they appear to have an elevated susceptibility to severe psychosis. Psychosis is particularly characteristic of spice after prolonged and heavy usage. The incidence of psychosis might be attributable to the absence of cannabidiol in synthetic blends. Cannabidiol is a natural marijuana coingestant with a postulated antipsychotic effect. Patients on synthetic cannabinoids have also been known to attempt suicide. The symptomomimetic effects of spice are also thought to be more exaggerated than marijuana intoxication. Features such as diaphoresis and mydriasis can accompany the mild tachycardia that is usually associated with marijuana. There is a high incidence of nausea and vomiting, pathomimetic effects of spice are also known to attempt suicide. Dystonia is another major feature.

Although half-life varies by individual compound, the relatively prolonged effect duration of synthetic cannabinoids is an additional distinguishing feature. JWH-081 has a half-life of 1 to 2 hours, and CP-47,497-C8 has a half-life of 5 to 6 hours. Less frequent but more severe symptoms commonly linked to spice abuse include seizures, cardiac ischemia, and acute kidney injury.

In addition to the distinctive acute effects of synthetic cannabinoids, spice drugs differ from THC in the incidence of addiction. Marijuana dependence is debated, and cannabis withdrawal is not included in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR).
because “symptoms of cannabis withdrawal... have been described... but their clinical significance is uncertain.”\textsuperscript{14} However, addiction to synthetic cathinones is well documented.\textsuperscript{10,15} Symptoms include nervousness, irritability, sleeping difficulties, strange dreams, and diaphoresis.\textsuperscript{15} It should be noted that these same symptoms are also cited in proposed criteria for marijuana addiction.\textsuperscript{14} A case report and anecdotal evidence further suggest that cravings for spice are an important component of withdrawal.\textsuperscript{15}

It is also necessary to consider that additives in the herbal blends can lead to unrelated and as yet uncharacterized clinical features.\textsuperscript{6}

\textbf{SYNTHETIC CATHINONES: Background}

The history of synthetic cathinones parallels that of synthetic cannabinoids. Synthetic cathinones are analogous to amphetamines and primarily demonstrate stimulant properties. Like synthetic cannabinoids, they were developed through research and have been introduced to consumers through masking-agent blends. The blends are referred to as “bath salts.” Synthetic cathinones are derived from a naturally occurring, long-standing psychotropic drug of abuse called “khat.”\textsuperscript{16}

The two synthetic cathinones that are the most prevalent in the United States are mephedrone (4-methylcathinone) and MDPV (3,4-methylenedioxyxymethamphetamine). Both were recently identified as related to khat (and the natural psychoactive chemicals cathinone and cathine), whose mention in medical literature dates back to the 11th century AD.\textsuperscript{1} Khat, which is widespread in East Africa and the Middle East, has recently become available in the United States and is infiltrating the worldwide drug market.\textsuperscript{1,16}

The first synthetic form of cathinone, known as methcathinone, was created in the 1930s but did not become a drug of abuse in the United States until the 1990s. Use of mephedrone, the initial bath salt drug, was first discovered in Europe in 2007 and appeared in the United States in 2009, followed soon after by MDPV. A third synthetic cathinone, methylone, is also prevalent in the United States.\textsuperscript{1}

Like synthetic cannabinoids, bath salts have also become a major drug of abuse in the United States. According to the American Association of Poison Control Centers, the number of calls related to bath salt exposure received by poison control centers across the country increased by more than 20-fold in 2011 alone, up from 304 incidents in 2010 to 6,138 in 2011. Bath salts are available at stores and over the Internet, but some compounds are now US Drug Enforcement Administration Schedule I controlled substances.\textsuperscript{2}

\textbf{Basic Science}

Synthetic cathinones are almost identical in structure to amphetamines, in some cases differing from drugs such as methamphetamine by only a carbonyl group\textsuperscript{1,8} (Figure 2). Their effects can be explained by the morphologic resemblance. Synthetic cathinones function by blocking the reuptake of dopamine, serotonin, and norepinephrine.\textsuperscript{1,8} To a lesser extent, they also increase the release of monoamines.\textsuperscript{1,8}

In the spectrum of effects, mephedrone favors dopamine reuptake inhibition, methylone has relatively minimal serotonergic effect, and mephedrone relatively strongly inhibits dopamine reuptake.\textsuperscript{13} The synthetic cathinones are more hydrophilic, less likely to cross the blood-brain barrier, and therefore are less potent than amphetamines;\textsuperscript{1} however, they are still lipophilic in absolute terms.\textsuperscript{13} They are typically ingested orally and are rapidly absorbed.

Mephedrone and methylone are often taken in doses of 100 to 200 mg and can cause psychoactive effects within 30 to 45 minutes. MDPV seems to be more potent and generates psychoactive effects within 15 to 30 minutes at a dose of 10 to 15 mg.\textsuperscript{1} In general, they produce a rush that peaks within 90 minutes and lasts 3 to 4 hours, resulting in an approximately 6- to 8-hour experience.\textsuperscript{17} The pharmacokinetics of mephedrone usually lead to clinical effects that can last more than 24 hours.\textsuperscript{8} MDPV can stimulate the central nervous system for 48 hours.\textsuperscript{13} At this point, it is unclear whether the duration of effect is attributable to redosing.\textsuperscript{7,18}

\textbf{Similarities to Amphetamines}

As amphetamine analogs, synthetic cathinones produce a “high” that is similar to methamphetamine. They tend to produce a sensation of euphoria, heightened alertness, increased energy, talkativeness, and sexual arousal. The latter two features might be particularly characteristic of mephedrone, which has been regarded as an analog of 3,4-methylenedioxy-N-methylamphetamine (MDMA, also known as “Ecstasy”). Mephedrone and MDMA belong to a class of substances called entactogens, which causes a person to emotionally identify with or feel connected to another, most likely due to the ability to acutely increase serotonin in the brain.\textsuperscript{13}

Coinciding with alertness and energy are additional sympathomimetic effects.
such as tachycardia, hypertension, hyperthermia, dehydration, mydriasis, and psychomotor agitation. Sympathomimetic toxicity is a common feature of amphetamine use, as it is with bath salts. Common adverse effects include tremor, trismus/bruxism, palpitations and chest pain, insomnia, and headache.\textsuperscript{8,11,16,18} The psychological effects of amphetamines — paranoia, hallucinations, anxiety, agitation, and violent behavior — are also characteristic of synthetic cathinones.\textsuperscript{13,18} Additionally, many severe, well-known adverse reactions of stimulants are linked to bath salt intoxication, including bath salt toxicity, cardiac rhythm monitoring and management.\textsuperscript{8} There is also a speculated link between khat and myocardial infarction.\textsuperscript{9} Other noted adverse effects of synthetic cathinones include cytotoxicity to hepatocytes and profound hypotremia leading to altered mental status, elevated intracranial pressure, and cerebral edema.\textsuperscript{13}

**TABLE 2. Basics of Clinical Management of Salvia and Piperazine Derivatives**

<table>
<thead>
<tr>
<th>Varieties/Names</th>
<th>Salvia</th>
<th>Piperazines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diviners Sage, Maria Pastora, Magic Mint, Mystic Sage</td>
<td>Benzo Fury, Head Rush, MDAI, Exotic Super Strong, XXX Strong as Hell</td>
<td></td>
</tr>
<tr>
<td>Clinical Effects</td>
<td>Hallucinations, antidepressant effects</td>
<td>Stimulant effects, hallucinations (at high doses), palpitations, anxiety, headache, vomiting, QT prolongation, seizures</td>
</tr>
<tr>
<td>Occasional tachycardia, hypertension, diuresis and nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection</td>
<td>GC-MS of urine/saliva</td>
<td>GC-MS of blood/urine, commercial ELISA assays for drugs of abuse</td>
</tr>
<tr>
<td>Management</td>
<td>Supportive care, users rarely present with salvia intoxication alone</td>
<td>Manage sympathomimetic toxicity, cardiac rhythm monitoring Benzodiazepines, IV fluids, and cooling</td>
</tr>
</tbody>
</table>

ELISA = enzyme-linked immunosorbent assay; GC-MS = gas chromatography–mass spectrometry; IV = intravenous.

**OTHER EMERGING DRUGS OF ABUSE**

**Salvia**

Salvia represents the reemergence of a drug used for centuries by the Mazatec people of Oaxaca, Mexico\textsuperscript{10} (Table 2). It is a plant product, now mostly smoked, with the hallucinogenic features of drugs such as LSD but with a novel mechanism of action mediated by kappa-opioid receptors rather than the serotonin system commonly targeted by hallucinogens.\textsuperscript{1,20} It is a nonalkaloid that is distinct from other known opioid receptor modulators.\textsuperscript{1} Salvia intoxication is characterized by intense hallucinations and a very short duration of a few minutes to 1 hour.\textsuperscript{1,20,21} There is a marked absence of clinically apparent physiologic changes, including no significant changes in heart rate and blood pressure.\textsuperscript{22} Some reports describe an association with substance-induced psychosis but rarely diuresis and nausea.\textsuperscript{21,23}

One special property of salvia is the possible extended antidepressant effect following intense hallucinations that has led to some interest in future therapeutic roles for the kappa-opioid activity is common in bath salt use, although there has been confusion in many cases about whether delusions and hallucinations represent outright psychosis or drug-induced delerium.\textsuperscript{8} Agitation has been reported in close to 80% of cases of synthetic cathinone toxicity according to observational data.\textsuperscript{13}
receptor system. At the same time, the impact of salvia on mood is still unclear. Addiction is not a prominent feature of salvia intoxication.

**Piperazines**

Piperazines are drugs with varying properties often used in combination to produce an effect similar to MDMA intoxication (Table 2). The most prevalent compounds are 1-benzylpiperazine (BZP) and 1-(3-trifluoromethylphenyl) piperazine (TFMPP). BZP is a weak amphetamine-like stimulant with non-unique sympathomimetic effects. It is mostly dopamine-mediated and tends to cause motor abnormalities when ingested in isolation. TFMPP is a serotonin-mediated hallucinogen that both modifies and is synergistic with the effects of BZP. It is not used in isolation and is no longer a controlled substance in the United States. As a coingestant, it blunts the motor dysregulation of BZP and results in a psychotropic effect similar to that of MDMA with stimulant, hallucinogenic, and entactogenic properties. Commonly reported symptoms and signs of intoxication include sympathetic hyperstimulation and vomiting, as well as the adverse effects of QT prolongation and seizures.

**“Foxy Methoxy”**

“Foxy Methoxy,” or 5-MeO-diisopropyltryptamine (5-MeO-DIPT), is a prevalent, relatively new drug of the tryptamine/alkyltryptamine family, ranked among the 10 most frequently identified drug items in five U.S. cities in 2011 according to SAMSHA. It is categorized, along with LSD, as an indoleamine (Figure 3). Closely related compounds include the ultra-short-acting hallucinogen DMT, or “businessman’s lunch,” and the herbal hallucinogen ayahuasca. Consistent with the other hallucinogens, it targets 5-HT receptors. Unlike similar drugs, Foxy Methoxy is also especially potent by mouth and has a sympathomimetic effect.

**Phenylethylamines**

The phenylethylamines, as distinct from indoleamines and piperazines, include the well-known compounds MDMA and mescaline. Others are now demonstrating wider prevalence; methylenedioxyamphetamine (MDA) was identified in limited volumes in 14 of the 23 reporting areas of SAMHSA in early 2011. Also growing in popularity are the “2C”-derivative psychedelic drugs, which resulted from the experimentation of Alexander Shulgin, PhD, in the 1970s and that have gained favor as legal alternatives to MDMA over the past few years. These drugs closely resemble MDMA and are hallucinogens, entactogens, and sympathomimetic agents.

**CONCLUSION**

The emerging synthetic cannabinoids and cathinones represent a novel health threat to the United States. Standard screening methods often do not facilitate diagnosis, but experience is beginning to reveal the clinical features of these drugs, and it is now possible to characterize their intoxication syndromes. With spice and bath salts, it is helpful that most signs and symptoms are similar to those of the well-known analog drugs they mimic. Other new drugs share characteristics with established intoxicants as well. Building on this foundation, we...
can be vigilant for the special and often alarming new features. Whether we achieve a lucid enough understanding of spice and bath salts to better address the thousands of ingestions or must instead turn our attention to the latest emerging drugs, we owe it to our patients to pause and take stock of our accumulating knowledge about the clinical presentation of all such drugs.

REFERENCES


