Emerging Drugs of Abuse: Clinical and Legal Considerations

ELIE G. AOUN, MD; PAUL P. CHRISTOPHER, MD; JAMES W. INGRAHAM, MD

ABSTRACT

Over the past several decades, nontraditional drugs of abuse, including bath salts, synthetic cannabinoids, and salvia, have increased in popularity and use. Despite this fact, they remain unfamiliar to many healthcare providers. Commonly marketed as "legal highs," these substances are being used for their desired neuropsychiatric effects, taking advantage of their accessibility, low cost, variable legality, and limited detection on traditional urine drug screens. Similar to traditional drugs of abuse, these substances have varying degrees of toxicity and may lead to potentially adverse effects, ranging from benign to life threatening. This paper offers a review of three of the more widely-used emerging drugs (or classes of drugs): bath salts, synthetic cannabinoids, and salvia. For each we review its history and development, the neurochemical basis for its clinical effects, the nature and route of ingestion, the range of desired effects, potential toxicities, diagnostic and therapeutic approaches, as well as social and legal considerations.

KEYWORDS: Emerging drugs, drug abuse, bath salts, salvia, synthetic cannabinoids

INTRODUCTION

The past decade has been witness to a growing number of drugs of abuse. These include designer drugs, which are synthesized to mimic the structure and/or psychoactive properties of existing substances, and herbal substances, which contain one or more molecules that elicit a range of psychoactive effects. The prevalence of the use of these drugs and a growing understanding of their toxicity has sparked concern among medical and public health professionals alike. Of additional concern is the manner in which many of these drugs are advertised and sold. They are commonly marketed as "legal highs" with packaging that appeals to youth and young adults, and are relatively inexpensive, readily available online, in "head shops," at gas stations and convenience stores, and are not detected by standard drug screens. Keeping legal regulations at pace with the development of these drugs has proved challenging. Although the Synthetic Drug Abuse Prevention Act of 2012 added 15 synthetic cannabinoid receptor agonists and 11 synthetic cathinones to Schedule I of the Controlled Substances Act,[1] new analogues continue to be developed to evade this and other state-specific bans.

This paper offers a review of three of the more widely-used emerging drugs (or classes of drugs): bath salts, synthetic cannabinoids, and salvia. For each substance, we will outline its history and development, the neurochemical basis for its clinical effects, the nature and route of ingestion, the range of desired effects, potential toxicities, diagnostic and therapeutic approaches, as well as social and legal considerations (**See Table 1**).

Bath salts

Background

'Bath salts' is a general term referring to more than 30 available synthetic derivatives of cathinone[2] which was identified in 1975 as the principal psychoactive component of Khat.[3]

Table 1. Summary of desired effects, toxicities and management

	Desired effects	Toxicities	Management
Bath salts	○ Stimulation ○ Elation ○ Friendliness ○ Fluency ○ Sexual arousal ○ Perceptual disturbances	○ Sympathetic overstimulation ○ Aggression ○ Agitation ○ Memory deficits ○ Hallucinations ○ Paranoia	○ Supportive measures ○ Low-stimulation environment ○ Benzodiazepines, ○ IV fluids ○ Brief low-dose antipsychotics for psychosis only
Synthetic cannabinoids	○ Euphoria ○ Relaxation ○ Disinhibition ○ Altered perception ○ Altered consciousness	○ Anxiety ○ Mood dysregulation ○ Memory deficits ○ Hallucinations ○ Paranoia ○ Seizures ○ Nausea/vomiting ○ Diaphoresis ○ Hot flushes ○ Mydriasis ○ Tremor ○ Tachycardia ○ Hypertension	○ Supportive measures ○ Low-stimulation environment ○ Benzodiazepines
Salvia	○ Trance-like state ○ Hallucinations ○ Sensory disturbances ○ Synesthesia ○ Extra-bodily experiences ○ Elevated mood	○ Depersonalization ○ Anxiety ○ Dysphoria ○ Confusion ○ Fear ○ Headaches ○ Drowsiness ○ Tachycardia ○ Hypertension	○ Supportive measures ○ Low-stimulation environments ○ Benzodiazepines

COURTESY OF DRUG ENFORCEMENT ADMINISTRATION (DEA)

Bath salts

Cathinones have been investigated for their stimulant, antidepressant and appetite suppressant properties, but such studies have been halted because of concerns for abuse and dependence.[2,3] Mephedrone, MDPV (3,4-methylenedioxypyrovalerone) and methylone are the most common recreationally-used cathinones because of their structural, and clinical, similarities with amphetamine.[4] They are most widely produced in China, Pakistan and India and are typically sold as powder or pellets. Bath salt can be administered by oral, intranasal, inhaled (smoked), intravenous, or rectal routes.[3]

Mechanism of action and neurochemical considerations

Bath salts exert their effects by inhibiting vesicular monoamine transporters for serotonin, dopamine and norepinephrine, thereby increasing presynaptic neurotransmitter levels.[5] They also act as potent monoamine oxidase (MAO) inhibitors, with increased selectivity for MAO-B.[6] When compared to amphetamine and MDMA, bath salts were found to produce a greater increase in serotonin and dopamine levels in the nucleus accumbens.[2]

Desired effects, toxicities and long term effects

Although the pharmacokinetic properties of bath salts vary with the specific analogue used, the average onset of subjective effects occurs within 30 minutes. Effects peak at 45 to 90 minutes after administration and last up to 3 hours. The subjective effects include stimulation, elation, friendliness, talkativeness, sexual arousal and perceptual disturbances.[7]

Adverse neurobehavioral reactions include anxiety, hallucinations, delusions (paranoid and other), agitation, aggression, impaired working memory, and bruxism.[4] Bath salts have also been associated with metabolic derangements including hyponatremia, rhabdomyolysis, disseminated intravascular coagulation, acute kidney injury, and hepatic failure.[4] Additional toxicities range from sympathetic overstimulation (including hypertension, tachycardia, and hyperthermia) to seizures and death.[4,8] Cases of excited delirium, known as "bath salts psychosis," have been reported and are associated with significant mortality.[8,9] Bath salts withdrawal symptoms include depression, impulsivity, anhedonia with cognitive complaints of poor concentration and attention.[15] Long-term bath salt use is complicated by tolerance and a marked tendency to re-dose, thereby increasing the risk for accidental overdose.[2]

Diagnostic and therapeutic considerations

Bath salts are not detected by standard urine toxicology tests. Mass spectroscopy and gas chromatography can be used to detect specific cathinones but these tests are expensive.[7] Result reporting from these methods is often delayed, making them less helpful in guiding differential diagnosis and treatment during the acute phase of illness.[7] At present, there are no validated guidelines for the management of acute bath salts intoxication but current recommendations include supportive measures, low stimulation environments, benzodiazepines for sedation and seizure prevention, and intravenous fluids for prevention of rhabdomyolysis.[10] More serious metabolic and hemodynamic adverse effects may require admission to a medical or intensive care unit. Brief courses of low-dose antipsychotics can be helpful in managing the psychotic symptoms of an excited delirium but prolonged use is discouraged.[11]

COURTESY OF DRUG ENFORCEMENT ADMINISTRATION (DEA)

K2/Spice

Synthetic cannabinoids (Spice)

Background

Synthetic cannabinoids, commonly referred to as "Spice" and "K2," act as agonists at the cannabinoid (CB) receptor.[7] These agents are synthesized and then sprayed on dried herbs that may possess their own implicit psychotropic properties. They are often marketed as "incense" and are typically labeled "not for human consumption" in order to circumvent the Controlled Substances Analogues Enforcement Act of the United States.[7] Synthetic cannabinoids were developed by independent laboratories following research

on the development of CB1/CB2 receptor agonists for the treatment of pain and nausea.[7] Similar to marijuana, they are ingested orally or smoked.

Mechanism of action and neurochemical considerations

Cannabinoid agonists vary in conformation and belong to specific structural groups. The most commonly identified analogues belong to the JWH (John W. Huffman), CP (Cyclohexyl Phenol) or HU (Hebrew University) structural groups.[7,12] Whereas THC is only a partial agonist at the CB1 and CB2 receptors, synthetic cannabinoids act as full agonists at these receptors with an affinity up to 800 times that of THC.[12] Cannabinoid receptors play a role in sensory perception and emotional processing of stimuli in the hippocampus, amygdala, and prefrontal cortex via reduction in GABA release and increase in dopamine and glutamate release.[13] In addition to CB receptor agonism, Spice products are often contaminated with Clenbuterol, which drives sympathetic nervous system activation via agonism at β2 adrenergic receptors.[7,13]

COURTESY OF DRUG ENFORCEMENT ADMINISTRATION (DEA)

K2/Spice

Desired effects, toxicities and long-term effects

The desired effects of synthetic cannabinoids closely resemble those of smoked and orally ingested marijuana, including euphoria, relaxation, disinhibition, and altered perception and consciousness.[7,13] Adverse reactions and toxic effects of synthetic cannabinoids result predominantly from activation of central CB receptors and β2 adrenergic receptors. Somatic and autonomic effects related to the cannabinoid toxidrome include nausea, vomiting, diaphoresis, hot flushes, xerostomia, mydriasis, tachycardia, hypertension, and tremors. Neuropsychiatric toxicities include anxiety, mood dysregulation, perceptual disturbances (hallucinations and delusions), memory impairment, sedation or psychomotor agitation, depersonalization, increased sensitivity to sensory stimuli, suicidal ideation, and seizures. Vascular reactivity and dysfunction have been reported in association with synthetic cannabinoid intoxication and is especially concerning in patients with a history of ischemic heart disease.[13] Tachyphylaxis has been described and is thought to be due to the long half-life of many of the synthetic cannabinoids and their active metabolites.[14] Clinical reports of deaths related to Spice intoxication and its complications are on the rise.[13,14]

Long-term Spice users may develop tolerance. Spice related withdrawal effects include sleep disturbances, seizures and cardiac conduction abnormalities with associated palpitations.[15] As with marijuana, there are several reports of new-onset psychosis following synthetic cannabinoid use that persists beyond the initial intoxication phase. Associated symptoms include paranoid and other delusions, disorganized speech and behavior, affective blunting, and waxing and waning psychomotor slowing. These symptoms may require inpatient management and treatment with antipsychotic medication. Thirty percent of these patients remained psychotic after eight months.[13-15] Other neuropsychiatric sequelae include depressed mood, neurovegetative dysfunction, and suicidal ideation.

Available evidence suggests that prolonged use of synthetic cannabinoids is more strongly associated with persistent psychosis than marijuana. This may be due to the higher affinity of these agents at CB1 and CB2 receptors, dose and potency variation of the active compounds found in synthetic cannabinoids, and the fact that natural cannabis contains cannabidiol, a compound with antipsychotic properties.[16,17]

Diagnostic and therapeutic considerations

Liquid gas chromatography tandem mass spectrometry (LC-MS/MS) and matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDY-TOF) are able to detect synthetic cannabinoids and their metabolites in urine.[13] Like bath salts, testing for synthetic cannabinoids requires use of specialty reference labs with related high costs and delays in reporting of results. There are no published guidelines for the management of the synthetic cannabinoid toxidrome but current recommendations include supportive care, provision of a low-stimulation environments, and use of benzodiazepines for anxiety and sedation.[7,13]

Salvia

Background

Unlike bath salts and synthetic cannabinoids, salvia (*salvia divinorum*) is a naturally occurring herb from the mint family that has been used in Mexico for centuries for its psychogenic effects.[18] Recreational use of salvia has surged over the last decade in the United States and Europe owing to its low cost, ease of purchase online, and a lack of legislation controlling its access and use. Salvia is most commonly smoked but can also be chewed with resulting mucosal absorption.[18]

Mechanism of action and neurochemical considerations

Salvinorin A has been identified as the active chemical responsible for salvia's clinical effects.[18] Salvinorin A is a diterpene compound with highly selective kappa opioid receptor agonist properties resulting in hallucinations, diuresis,

mood improvement and spinal analgesia. In contrast to μ opioid receptor agonists, diterpenes are not associated with respiratory depression. The kappa receptor has been extensively researched for its antidepressant and anxiolytic properties, making it unclear why salvia can produce a paradoxical increase in anxiety.[19,20] The onset and duration of salvia's effects depend upon the route of administration and range from minutes to up to an hour. [20] Salvia is hepatically metabolized by the cytochrome oxidase isoenzyme system and undergoes first pass metabolism, explaining why oral ingestion does not produce neuropsychiatric effects.[20]

Desired effects, toxicities and long-term effects

The desired effects of salvia include a state of "trance" or "reminiscent meditation" that is similar to that produced by lysergic acid diethylamide (LSD), ketamine, and cannabis.[21] The intoxication state is marked by hallucinations, other sensory-perceptual distortions, increased sensitivity to sensory stimuli, synesthesia, out-of-body experiences, and mood elevation.[18,21] Unwanted effects of salvia intoxication include anxiety, dysphoria, confusion, language impairments and fear associated with "bad trips." Symptoms of headaches and drowsiness have been reported to last for several hours after the most recent use.[18] Withdrawal episodes marked by tachycardia and hypertension have been described but these are uncommon.[19] Cases of persistent psychosis in the setting of chronic use have been described and it has been suggested that salvia can unmask or exacerbate preexisting mental illness.[19,21] Cases of salvia addiction have been reported but its prevalence has not been studied.[21]

Diagnostic and therapeutic considerations

Similar to synthetic cannabinoids and bath salts, salvia testing is not part of routine urine drug screens. It, too, can be detected by the use of high-performance liquid chromatography (HPLC) LC–MS/MS or gas chromatography–mass spectrometry (GC–MS) – but with related high cost and delayed result reporting. It remains uncommon for a patient to seek medical care solely for salvia intoxication, but current management recommendations include supportive care treatment with benzodiazepines as indicated for agitation or severe anxiety.[19]

CONCLUSION

Bath salts, synthetic cannabinoids, and salvia are three novel agents in a constantly evolving list of drugs of abuse. Abuse of these substances is particularly worrisome because they are readily available, inexpensive, perceived as harmless by the general public, result in severe somatic and neuropsychiatric toxidromes, and because they are not readily detected by routine drug screening methods. Despite the protean and severe effects of the toxidromes associated with these drugs, medical professionals may be unfamiliar with their presentation and management. The adverse effects of these

COURTESY OF NATIONAL INSTITUTE OF DRUG ABUSE

Salvia

and other novel drugs of abuse have been made clear on a local level with a recent report from the Rhode Island Department of Health of 10 deaths from Acetyl-Fentanyl overdose, a fentanyl analogue that is up to five times more potent than heroin. These drugs pose unique challenges to the medical community and regulatory bodies, as advancements in molecular chemistry have paved the way for the continuous development of newer and more potent substances of abuse.

References

1. United States Government Printing Office (2012) S. 3190 (IS) – Synthetic Drug Abuse Prevention Act of 2012. http://www.gpo.gov/fdsys/search/pagedetails.action?packageId=-BILLS-112s3190is. Accessed Sept 1st 2013.
2. Kelly JP. Cathinone derivatives: a review of their chemistry, pharmacology and toxicology. *Drug Test Anal.* 2011 Jul-Aug;3(7-8):439-453. United States Government Printing Office (2012).
3. Capriola M. Synthetic cathinone abuse. *Clin Pharmacol.* 2013 Jul 2;5:109-115.
4. Spiller HA, Ryan ML, Weston RG, Jansen J. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin Toxicol (Phila).* 2011 Jul;49(6):499-505.
5. López-Arnau R, Martínez-Clemente J, Pubill D, Escubedo E, Camarasa J. Comparative neuropharmacology of three psychostimulant cathinone derivatives: butylone, mephedrone and methylone. *Br J Pharmacol.* 2012 Sep;167(2):407-420.
6. Schifano F, Albanese A, Fergus S, Stair JL, Deluca P, Corazza O, Davey Z, Corkery J, Siemann H, Scherbaum N, Farre' M, Torrens M, Demetrovics Z, Ghodse AH; Psychonaut Web Mapping; ReDNet Research Groups. Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. *Psychopharmacology (Berl).* 2011 Apr;214(3):593-602.
7. Loeffler G, Hurst D, Penn A, Yung K. Spice, bath salts, and the U.S. military: the emergence of synthetic cannabinoid receptor agonists and cathinones in the U.S. Armed Forces. *Mil Med.* 2012 Sep;177(9):1041-1048.
8. Wood DM, Greene SL, Dargan PI. Clinical pattern of toxicity associated with the novel synthetic cathinone mephedrone. *Emerg Med J.* 2011 Apr;28(4):280-282.

9. Joksovic P, Mellos N, van Wattum PJ, Chiles C. "Bath salts" – induced psychosis and serotonin toxicity. *J Clin Psychiatry.* 2012 Aug;73(8):1125.
10. Ross EA, Watson M, Goldberger B. "Bath salts" intoxication. *N Engl J Med.* 2011 Sep 8;365(10):967-968.
11. Vilke GM, DeBard ML, Chan TC, Ho JD, Dawes DM, Hall C, Curtis MD, Costello MW, Mash DC, Coffman SR, McMullen MJ, Metzger JC, Roberts JR, Sztajnkrcer MD, Henderson SO, Adler J, Czarnecki F, Heck J, Bozeman WP. Excited Delirium Syndrome (ExDS): defining based on a review of the literature. *J Emerg Med.* 2012 Nov;43(5):897-905.
12. Weissman A, Milne GM, Melvin LS Jr. Cannabimimetic activity from CP-47,497, a derivative of 3-phenylcyclohexanol. *J Pharmacol Exp Ther.* 1982 Nov;223(2):516-523.
13. Seely KA, Lapoint J, Moran JH, Fattore L. Spice drugs are more than harmless herbal blends: a review of the pharmacology and toxicology of synthetic cannabinoids. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012 Dec 3;39(2):234-243.
14. Wells DL, Ott CA. The "new" marijuana. *Ann Pharmacother.* 2011 Mar;45(3):414-417.
15. Biliński P, Hołownia P, Kapka-Skrzypczak L, Wojtyła A. Designer Drug (DD) abuse in Poland; a review of the psychoactive and toxic properties of substances found from seizures of illegal drug products and the legal consequences thereof. Part 1--cannabinoids and cathinones. *Ann Agric Environ Med.* 2012;19(4):857-870.
16. da Silva VK, de Freitas BS, da Silva Dornelles A, Nery LR, Falavigna L, Ferreira RD, Bogo MR, Hallak JE, Zuardi AW, Crippa JA, Schröder N. Cannabidiol Normalizes Caspase 3, Synaptophysin, and Mitochondrial Fission Protein DNM1L Expression Levels in Rats with Brain Iron Overload: Implications for Neuroprotection. *Mol Neurobiol.* 2013 Jul 28. [Epub ahead of print]
17. Atwood BK, Lee D, Straiker A, Widlanski TS, Mackie K. CP47,497-C8 and JWH073, commonly found in 'Spice' herbal blends, are potent and efficacious CB(1) cannabinoid receptor agonists. *Eur J Pharmacol.* 2011 Jun 1;659(2-3):139-145.
18. Kelly BC. Legally tripping: a qualitative profile of Salvia divinorum use among young adults. *J Psychoact Drug.* 2011 Jan-Mar; 43(1):46-54.
19. 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 Mar;8(1):15-32.
20. Aviello G, Borrelli F, Guida F, Romano B, Lewellyn K, De Chiaro M, Luongo L, Zjawiony JK, Maione S, Izzo AA, Capasso R. Ultrapotent effects of salvinorin A, a hallucinogenic compound from Salvia divinorum, on LPS-stimulated murine macrophages and its anti-inflammatory action in vivo. *J Mol Med (Berl).* 2011 Sep;89(9):891-902.
21. Baggott MJ, Erowid E, Erowid F, Galloway GP, Mendelson J. Use patterns and self-reported effects of Salvia divinorum: an internet-based survey. *Drug Alcohol Depend.* 2010 Oct 1;111(3): 250-256.

Authors

Elie G. Aoun, MD, is a Resident in the Adult Psychiatry Residency Program at the Alpert Medical School of Brown University and Butler Hospital, Providence, RI.

Paul P. Christopher, MD, is an Assistant Professor, Dept. of Psychiatry & Human Behavior at the Alpert Medical School of Brown University and Butler Hospital, Providence, RI.

James W. Ingraham, MD, is a Psychiatrist affiliated with the Alpert Medical School of Brown University and Butler Hospital, Providence, RI.

Correspondence

Elie G. Aoun, MD
Butler Hospital
345 Blackstone Blvd.
Providence RI 02906
Elie_aoun@brown.edu