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Novel Drugs of Abuse: A Snapshot of an Evolving Marketplace

Ryan Vandrey, Matthew W. Johnson, Patrick S. Johnson, and Miral A. Khalil

Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Background & objectives—Over the past decade, non-medical use of novel drugs has proliferated worldwide. In most cases these are synthetic drugs first synthesized in academic or pharmaceutical laboratories for research or drug development purposes, but also include naturally occurring substances that do not fit the typical pharmacological or behavioral profile of traditional illicit substances. Perhaps most unique to this generation of new drugs is that they are being sold over the counter and on the Internet as “legal highs” or substitutes for traditional illicit drugs such as cannabis, cocaine, amphetamines, MDMA, and LSD. The purpose of this review is to provide an overview of novel drugs in current use, including the epidemiology of use and toxicologic and pharmacological properties, and to offer some guidelines to clinicians who see patients experiencing adverse effects from these drugs.

Method—We review the known scientific literature on recently introduced synthetic drug types, synthetic cannabinoids and synthetic cathinones, and the hallucinogen *Salvia divinorum*.

Results—These substances comprise part of a rapidly evolving and controversial drug market that has challenged definitions of what is legal and illegal, has benefitted from open commercial sales without regulatory oversight, and is noteworthy for the pace at which new substances are introduced.

Conclusions—This emerging trend in substance use presents significant and unique public health and criminal justice challenges. At this time, these substances are not detected in routine drug screens and substance-specific treatment for cases of use-related toxicity are not available. Clinicians are encouraged to learn characteristic signs associated with misuse of novel drugs to recognize cases in their practice, and are recommended to use a symptom-specific approach for treatment in each case.

Keywords

Synthetic drugs; cannabinoids; cathinones; *Salvia divinorum*; Salvonirin A; Spice; Bath Salts

Address correspondence to this author at the Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, 5510 Nathan Shock Dr. Baltimore, MD 21224, 410-550-4036 (phone); 410-550-0030 (fax), rvandrey@jhmi.edu.

Drs. Vandrey and M. Johnson are faculty at the Johns Hopkins University Behavioral Pharmacology Research Unit. They are behavioral pharmacologists with expertise in the conduct of human laboratory and clinical research related to the use of psychoactive drugs and analysis of behavior. Drs. P Johnson and Khalil are post-doctoral trainees at the Johns Hopkins University Behavioral Pharmacology Research Unit. Dr. P. Johnson is an experimental psychologist and behavior analyst. Dr. Khalil is a physician with an interest in clinical care and research related to addictions.

Conflict of Interest

The authors have no financial or other conflicts of interest to report.

INTRODUCTION

Substance abuse has been a longstanding public health problem and is associated with substantial societal costs. Historically, drug use has been confined to a relatively limited number of drugs that were mostly well known (e.g. alcohol, amphetamines, cannabis, cocaine, heroin, LSD). Across generations, the popularity of certain drugs or drug classes tends to change and periodically new drugs or formulations of known drugs have been introduced resulting in a new fad or “epidemic” of drug use. Examples of this include “crack” cocaine in the 1980s, MDMA (ecstasy) in the 1990s, and, more recently, methamphetamine and prescription opioids. However, in the last few years, the number of new drugs being introduced to the non-medical drug market has drastically accelerated. In fact, the number of new drugs detected for the first time in Europe increased from 24 in 2009 to 41 in 2010, 49 in 2011 and over 50 new drugs in 2012 (EMCDDA, 2012).

In addition to the volume at which new illicit drugs are being introduced, the manner in which they are being produced and sold also marks a dramatic shift from the past. In prior generations, new drugs were introduced through established illegal drug supply networks and/or were medications diverted from medical use due to their reinforcing/intoxicating properties. Many of the current generation of drugs, however, have been (and in some cases still are) sold in retail stores (gas stations, convenience stores, alternative lifestyle “head” shops) and over the Internet with bold marketing geared towards youth and young adults. In some cases, such as that of *Salvia divinorum*, a plant with hallucinogenic effects, the drugs are openly sold. However, in most cases, the drugs are disguised in packages that do not list the drug contents, and suggest that the products are to be used as “incense” or “bath salts,” and are “not for human consumption” as a means of circumventing drug laws and regulation. However, use of these products as intoxicants is openly described on Internet forums and chat rooms dedicated to drug use, and in many cases is inferred from some brand names and labeling (e.g. Tai High, Bliss, AM-HI, Ex-Ses).

Here we provide a review of the predominant substances that comprise this new generation of “recreational” drugs: synthetic cannabinoids, synthetic cathinones, and *Salvia divinorum*. In addition to these substances, a number of previously unknown hallucinogens (phenethylamines and tryptamines), synthetic cocaine derivatives, piperazines (psychostimulants), ketamine derivatives (dissociative anesthetics), and plant products (e.g., *Mitragyna speciosa*, a.k.a. kratom) have also been detected, but to date there is insufficient scientific and/or published clinical data to adequately address these in the present manuscript.

SYNTHETIC CANNABINOIDS

“Synthetic cannabinoids” is a generic term for compounds that bind to and activate endogenous cannabinoid receptors, the same receptor system as delta-9-tetrahydrocannabinol (THC), the primary psychoactive constituent of cannabis/marijuana (Mechoulam & Gaoni, 1967). Among these are a number of compounds that are potent agonists of the cannabinoid 1 (CB1) receptor, which mediates the reinforcing and intoxicating effects of cannabis (Mechoulam, Shani, Edery, & Grunfeld, 1970; Wiley,

Compton, Dai, Lainton, Phillips, Huffman et al., 1998; Wiley, Jefferson, Grier, Mahadevan, Razdan, & Martin, 2001), and are now being discovered in commercial products used as legal alternatives to cannabis. Sold primarily as “herbal blends” or “incense” products under a variety of brand names (Spice and K2 being prominent), synthetic cannabinoids are widely available in stores (head shops, convenience stores, and gas stations) and over the Internet. Products most commonly consist of inert dried plant material such as wild dagga, marshmallow, and damiana, which is used as a vehicle for delivering one or more synthetic cannabinoids, though raw chemicals can also be purchased/used without the plant material (Vandrey, Dunn, Fry, & Girling, 2012; Vardakou, Pistos, & Spiliopoulou, 2010). Synthetic cannabinoid products are most commonly smoked, though administration via oral consumption and anal insertion have also been reported (Vandrey, et al., 2012).

The synthetic cannabinoids detected in commercial products primarily originated from the laboratories of John W. Huffman (JWH compounds), Pfizer Inc. (CP compounds), Hebrew University (HU compounds), and Alexandros Makriyannis (AM compounds) and consist of seven distinct structural groups: naphthoylindoles, naphthylmethylindoles, naphthoylpyrroles, naphthylmethylenes, phenylacetylindoles, cyclohexylphenols, and classical cannabinoids (Ernst, Kruger, Lindigkeit, Schiebel, & Beuerle, 2012; Fattore & Fratta, 2011; Rosenbaum, Carreiro, & Babu, 2012). Recently, previously uncharacterized chemicals have been discovered suggesting that the chemists responsible for this market have begun to create entirely new compounds (Jankovics, Varadi, Tolgyesi, Lohner, Nemeth-Palotas, & Balla, 2012; Simolka, Lindigkeit, Schiebel, Papke, Ernst, & Beuerle, 2012; Uchiyama, Kikura-Hanajiri, & Goda, 2011).

Because the packaging of synthetic cannabinoid products are intentionally misleading (packaged as “incense” or “potpourri” and labeled as “not for human consumption”), the actual chemical contents are generally unknown to users, clinicians and law enforcement. Forensic toxicology testing on purchased/seized products and samples obtained from hospital patients presenting with adverse effects following use has been conducted to identify the chemical constituents of synthetic cannabinoid products (Auwärter, Dresen, Weinmann, Muller, Putz, & Ferreiros, 2009; Dresen, Ferreiros, Putz, Westphal, Zimmermann, & Auwarter, 2010; Ernst, et al., 2012; Lindigkeit, Boehme, Eiserloh, Luebbecke, Wiggermann, Ernst, 2009; Simolka, et al., 2012; Uchiyama, et al., 2011). Based on this testing, and growing public health concerns associated with these drugs, several specific compounds are now regulated under various national and local drug control laws. It seems, however, that regulation of known compounds is directly related to the proliferation of new compounds on the market (Ernst, et al., 2012).

Epidemiology of Synthetic Cannabinoids

Use of “herbal incense” products now known to contain synthetic cannabinoids can be traced back as early as 2006 in public posts on drug-related websites such as www.drugs-forum.com. Academic publications, government reports, and wide-ranging media reports suggest that synthetic cannabinoids have been marketed in most developed countries. Unfortunately, due the time lag between identification of new drug trends and incorporation into large-scale epidemiological surveys, data on the prevalence of synthetic cannabinoid

use is scarce. Data from several European survey studies suggest that rates of use for “legal highs” and synthetic cannabinoids are highest among the 15–24 year old demographic, in which 5–6% of respondents indicated lifetime use (EMCDDA, 2012a). Rates of use varied by country with the highest prevalence of “legal highs” being 16% among 15–24 year olds in Ireland. In contrast, lifetime use was only 1% among 14–18 year-olds in a separate survey of school aged youth in Spain.

In the U.S., past year use of synthetic cannabinoids is estimated at 4%, 9%, and 11% of students in the 8th, 10th, and 12th grades respectively (Johnston, O’Malley, Bachman, & Schulenberg, 2012). The 11% use rate among 12th graders remained the same in the 2011 and 2012 surveys (8th and 10th graders were not screened in 2011). In 2010, synthetic cannabinoids were associated with 11,406 emergency hospital admissions (SAMHSA, 2012). Of those, 75% were aged 12–29 and 78% were male. Perhaps the best source for tracking the development of synthetic cannabinoid use in the U.S. have been reports of The American Association of Poison Control Centers (AAPCC). Calls to the AAPCC increased from 13 calls in 2009 to 2,906 calls in 2010 including calls from 49 of the 50 U.S. states and the District of Columbia indicating a rapid and geographically broad adoption in use (AAPCC, 2010). The number of calls to AAPCC then escalated to 6,959 in 2011 and numbered 5,200 in 2012 (AAPCC, 2012b). We were not able to find representative assessments of use for other countries.

Informal reviews of Internet websites and media reports indicate that synthetic cannabinoid use proliferated initially because users believed the products were safe, legal alternatives to cannabis, and that they offer a means to achieve the subjective effects of cannabis without detection in standard urine toxicology tests (Vardakou, et al., 2010). For these reasons, synthetic cannabinoid use was initially popular among those subject to drug testing (e.g. student athletes, those involved with criminal justice system, and military/government employees). More recent survey studies suggest that curiosity, more convenient availability, and preference for the effects of synthetic cannabinoids compared with other drugs are also common reasons for use (Barratt, Cakic, & Lenton, 2012; Vandrey, et al., 2012).

Toxicology of Synthetic Cannabinoids

Initial identification of synthetic cannabinoid compounds in these “Spice” products was achieved by German scientists in 2008 (Auwärter, et al., 2009). To date, over 40 different substances characterized as synthetic cannabinoids have been identified in products such as “Spice,” “K2,” and “Kronic” (EMCDDA, 2012a). For the first few years, a core group of compounds were frequently detected in synthetic cannabinoid products including JWH-018, JWH-073, JWH-250, JWH-398, CP 47,497, and HU-210 (Dresen, et al., 2010; Lindigkeit, et al., 2009; Vardakou, et al., 2010). Subsequent to the placing of these compounds on schedules of illegal substances in many countries, there has been a rapid influx of new compounds to the market and many products contain multiple synthetic cannabinoids (Dresen, et al., 2010; Shanks, Dahn, Behonick, & Terrell, 2012; Simolka, et al., 2012). Despite this, product testing has indicated that some banned substances, JWH-018 in particular, remain present in many commercially sold products, even where illegal and product labeling explicitly states the product is in compliance with local laws (Boos, 2011;

Ernst, et al., 2012; Shanks, et al., 2012). Also of interest is that there appears to be substantial variability in the specific compounds and concentrations of the synthetic cannabinoids found in commercial products, even within the same “brand” (Auwärter, et al., 2009; Dresen, et al., 2010). Such inconsistencies in product preparation can make dose titration difficult for users.

Assays for detecting synthetic cannabinoids and their metabolites in biological fluids (e.g. urine, oral fluid) have been developed (Coulter, Garnier, & Moore, 2011; ElSohly, Gul, Elsohly, Murphy, Madgula, & Khan, 2011; Heltsley, Shelby, Crouch, Black, Robert, Marshall, et al., 2012; Kneisel, Auwarter, & Kempf, 2012). However, these methods are limited to complex and expensive analytic methods (e.g. high-performance liquid chromatography—tandem mass spectrometry), and are limited to large laboratories that have the standards to detect the ever-increasing number of synthetic cannabinoids on the market. This limits the ability to conduct drug testing for these substances in clinical settings relative to testing for more established drugs such as cannabis, for which rapid, on-site drug screening products are available. As a result, few health care or workplace programs have the resources to conduct diligent drug monitoring of these compounds. In addition, even with the most sophisticated technologies at hand, interpretation of test results can be difficult because little is known about the rate of elimination or window of detection for these compounds and their various metabolites in any biological matrix.

Pharmacology of Synthetic Cannaboids

The common pharmacological feature of the synthetic cannabinoids detected in commercial Spice/K2/Kronic products is that they are all potent agonists of the CB1 receptor. Controlled research on the effects of these compounds mostly consist of preclinical studies assessing cannabinoid receptor binding affinity and *in vivo* effects on the “cannabinoid tetrad,” a series of four assessments (analgesia, catalepsy, hypomobility, and hypothermia) conducted with mice that are reliably associated with CB1 agonist drugs such as THC (Wiley, et al., 1998). These studies have shown that many of the synthetic cannabinoids detected on the street have an affinity for the CB1 receptor that is equal and up to five times greater than THC (Aung, Griffin, Huffman, Wu, Keel, Yang, et al., 2000; Wiley, et al., 1998; Wiley, Marusich, Martin, & Huffman, 2011). Similarly, these compounds show comparable or greater potency compared with THC on the classical cannabinoid tetrad tests (Aung, et al., 2000; Brents, Gallus-Zawada, Radomska-Pandya, Vasiljevik, Prinszano, Fantegrossi, et al., 2012; Brents, Reichard, Zimmerman, Moran, Fantegrossi, & Prather, 2011; Wiley, et al., 1998; Wiley, et al., 2011). Interestingly, JWH-018 and JWH-073 were found to have several metabolites with high CB1 receptor affinities that are behaviorally active (Brents, et al., 2012; Brents, et al., 2011). A study conducted with non-human primates also showed that JWH-018 and JWH-073 dose-dependently substituted for THC in a drug discrimination paradigm, and that the duration of effects for both synthetic drugs was significantly shorter than THC (Ginsburg, Schulze, Hrubá, & McMahon, 2012). Consistent with these preclinical findings, case reports and surveys of human synthetic cannabinoid users confirm that use produces effects that are very similar to cannabis and include: feeling high/euphoric, dissociation/dream-like state, tired/sluggish, lightheaded, increased appetite, dry mouth, increased heart rate, paranoia (Barratt, et al., 2012; Vandrey, et al., 2012).

Clinical Consequences—There is clear evidence that synthetic cannabinoid use can be problematic. Case reports suggest that tolerance develops quickly and withdrawal can occur following chronic use (Vandrey, et al., 2012; Zimmermann, Winkelmann, Pilhatsch, Nees, Spanagel, & Schulz, 2009). In the U.S., thousands of calls to poison control centers and hospital admissions have been associated with acute use of synthetic cannabinoids (AAPCC, 2012b; SAMHSA, 2012). Hoyte and colleagues recently published a report summarizing 1353 emergency response cases handled by U.S. poison control centers in which callers reported adverse effects following acute use of synthetic cannabinoids in the absence of other drugs (Hoyte, Jacob, Monte, Al-Jumaan, Bronstein, & Heard, 2012). The most common clinical effects reported were: tachycardia (40%), agitation/irritability (23%), vomiting (15%), drowsiness/lethargy (14%), confusion (12%), nausea (10%), hallucinations/delusions (9%), hypertension (8%), dizziness/vertigo (7%), and chest pain (5%). Seven percent of cases were documented as “potentially life threatening,” 52 cases involving seizures were reported, and a 58 year-old male died of cardiac arrest following use. Clinical effects resolved in less than 8 hours in 78% of the cases, and within 24 hours for 95% of cases. Additional published case reports are available that provide more detailed accounts of similar cases (Faircloth, Khandheria, & Shum, 2012; Harris & Brown, 2012; Lapoint, James, Moran, Nelson, Hoffman, & Moran, 2011; Simmons, Skinner, Williams, Kang, Schwartz, & Wills, 2011). In addition, other cases have been documented where use of synthetic cannabinoids was associated with a recurrence or exacerbation of ongoing psychosis in patients with previously diagnosed psychiatric illness (Müller, et al., 2010), new-onset psychosis lasting 6–10 days (Hurst, Loeffler, & McLay, 2011), loss of loco-motor control (Harris & Brown, 2012), and intracranial haemorrhage (Kamat, Aliashkevich, Denton, & Fitzjohn, 2012). There are no pharmacologically specific treatments available for managing adverse reactions to synthetic cannabinoids, rather, clinicians must assess each case and develop a symptom-specific treatment strategy.

Synthetic Cathinones

Synthetic cathinones (sometimes referred to as “beta-ketones”) emerged around the same time as synthetic cannabinoids and appear to have been developed as “legal” alternatives to illicit psychostimulant drugs (e.g. cocaine, amphetamines, MDMA) in the same manner that synthetic cannabinoids served as surrogates for cannabis. Synthetic cathinone containing products are typically sold on the Internet and in retail stores as “bath salts,” “plant food,” “glass cleaner,” or “research chemicals” (Murphy, Dulaney, Beuhler, & Kacinko, 2012; Spiller, Ryan, Weston, & Jansen, 2011). Chemically related to cathinone, a naturally occurring stimulant found in *Catha edulis* (khat), these drugs are primarily sympathomimetic in their action (Mas-Morey, Visser, Winkelmann, & Touw, 2012). The primary route of administration is intranasal, but oral, smoked, intravenous, and rectal routes of administration have also been reported (Carhart-Harris, King, & Nutt, 2011; Winstock, Mitcheson, Ramsey, Davies, Puchnarewicz, & Marsden, 2011).

The three most well known synthetic cathinones are 4-methylmethcathinone (mephedrone), 3,4-methylenedioxypyrovalerone (MDPV), and 3,4-methylenedioxymethylmethcathinone (methyldone). These were the primary compounds found in initial commercial products, but are now widely regulated in national and/or local drug control laws due to adverse health

consequences associated with their use (Fass, Fass, & Garcia, 2012). Despite the widespread scheduling of these initial substances, synthetic cathinone products and their constituent ingredients continue to pose a serious public health risk because novel “second generation” drugs continue to surface in commercial products as a means of eluding drug control laws, and the primary initial substances remain in use in illegal drug markets where banned (EMCDDA, 2012a; Shanks, et al., 2012).

Epidemiology—Non-medical use of synthetic cathinones began with the rapid adoption of mephedrone in 2009 in northern Europe, particularly in the night-club and dance music scenes in the United Kingdom (UK) where it was used as a then-legal substitute for illegal stimulants such as 3,4-methylenedioxymethylamphetamine (MDMA, ecstasy) and cocaine (Dargan, Albert, & Wood, 2010; McElrath & O'Neill, 2011). Mephedrone users tended to be young males (e.g., 25 years) with polydrug experience (Carhart-Harris, et al., 2011; Winstock, et al., 2011). In April 2010, mephedrone was classified in the UK as a Class B drug under the Misuse of Drugs Act 1971 (<http://www.legislation.gov.uk/ukpga/1971/38/contents>), and similar regulations were enacted by the European Union soon thereafter. Following these control efforts, mephedrone users reported decreases in the quality of the drug and increased pricing by street-level dealers (Winstock, Mitcheson, & Marsden, 2010). Mephedrone-related emergency department presentations also decreased subsequent to scheduling, although additional research is needed to determine if overall use decreased and the role of increased regulation in this decline (Wood, Greene, & Dargan, 2013). Synthetic cathinone products spread to the U.S. and other countries by 2010, and the trajectory of synthetic cathinone regulation has been similar, with localized bans having some success limiting the sale of products in retail stores, but with apparently little effect on Internet-based markets (Ayres & Bond, 2012; Shanks, et al., 2012).

As with the synthetic cannabinoids, there remains a paucity of epidemiological data from large representative surveys to characterize the use of synthetic cathinones. Lifetime use of mephedrone use was estimated at 2% of people aged 15–64 and 6% of those aged 15–24 in a survey conducted in Northern Ireland, while past year use in the UK in 2010/11 was estimated at 1% for those aged 15–59 and 4% of 16–24 year olds (EMCDDA, 2012a). In the U.S., use of synthetic cathinone products among students was estimated at 0.8%, 0.6%, and 1.3% for grades 8, 10, and 12, respectively (Johnston, et al., 2012). In the U.S., calls to poison control centers are greatest among persons aged 20–29 and increased from 304 in 2010 to 6,138 in 2011 indicating the rapid uptake of use in 2011 (AAPCC, 2012a). Calls in 2012 numbered only 2,654, possibly indicating a reduction in use compared with 2011 (AAPCC, 2012a).

Toxicology—To date, over 30 different substances characterized as synthetic cathinones have been identified in “bath salts” products with names such as Vanilla Sky and Ivory Wave (EMCDDA, 2012a). Before laws were enacted to control the availability and use of these products, mephedrone was the predominant synthetic cathinone in the UK, while MDPV was predominant in the U.S. (Shanks, et al., 2012; Spiller, et al., 2011). Second generation synthetic cathinones include alpha-PVP, butylone, buphedrone, methylene,

naphyrone, and methedrone (EMCDDA, 2012b; Mas-Morey, et al., 2012; Rosenbaum, et al., 2012; Shanks, et al., 2012; Zuba, Adamowicz, & Byrska, 2012).

Detection of use in biological fluids (e.g. urine, blood, oral fluid) can be conducted with sophisticated analytic methods (e.g. gas chromatography/mass spectrometry or liquid chromatography/mass spectrometry) in laboratories that have access to synthetic cathinone standards (Mas-Morey, et al., 2012; Strano-Rossi, Anzillotti, Castrignano, Romolo, & Chiarotti, 2012; Zuba, et al., 2012). However, data are lacking regarding the rate of elimination, window of detection, target metabolites, or association of drug/metabolite concentration with clinical effects in humans for synthetic cathinones in any biological matrix. Further complicating matters is a recent report suggesting that MDPV provides false-positive results on PCP immunoassays (Macher & Penders, 2012).

Pharmacology—Recent experimental data have begun to elucidate the pharmacological mechanisms and effects of select synthetic cathinones. Mephedrone, MDPV, methylone, ethylone, butylone and naphyrone have been shown to be non-selective monoamine uptake inhibitors, similar to cocaine, whereas, mephedrone, methylone, ethylone and butylone also act as transporter substrates inducing the release of serotonin (5-HT) in a manner similar to MDMA (ecstasy; Baumann, Partilla, Lehner, Thorndike, Hoffman, Holy, et al., 2012; Simmler, Buser, Donzelli, Schramm, Dieu, Huwyler, et al., 2013). Cathinone and its analog methcathinone are structurally related to amphetamine, and these substances and their synthetic derivatives exhibit classic stimulant-like neuropharmacological profiles. For example, synthetic cathinones have been shown to increase motor behavior at comparable levels as cocaine and methamphetamine (Baumann, et al., 2012; Fantegrossi, Gannon, Zimmerman, & Rice, 2012; Marusich, Grant, Blough, & Wiley, 2012).

However, there are also unique characteristics with regards to specific effects and potency. For example, rats self-administer MDPV at levels similar to methamphetamine (Watterson, Kufahl, Nemirovsky, Sewalia, Grabenauer, Thomas, et al., 2012), but MDPV is also at least 10 times more potent than cocaine in inducing increased motor activity, tachycardia, and hypertension in rats (Baumann, et al., 2012). Mephedrone, but not MDPV, induces hypothermia at lower ambient temperatures and hyperthermia at higher ambient temperatures in a manner similar to MDMA (Fantegrossi, et al., 2012). Similarly, an experiment evaluating wheel running behavior suggests that MDPV displayed dose-related effects comparable to typical psychomotor stimulants (inverted u-shaped curve), but that mephedrone was more like MDMA in producing a mono-phasic, dose-dependent reduction in wheel running (Huang, Aarde, Angrish, Houseknecht, Dickerson, & Taffe, 2012). Interestingly though, both MDMA and methamphetamine fully substituted for MDPV in a drug discrimination study conducted with mice (Fantegrossi, et al., 2012).

Controlled behavioral pharmacology research is currently lacking with these substances, but retrospective case reports and surveys indicate that acute effects of synthetic cathinones generally include increased energy, euphoria, talkativeness, urge to move or do things, increased libido, empathy, bruxism, sweating, loss of appetite and insomnia (Prosser & Nelson, 2012; Winstock, et al., 2011).

Clinical Consequences—Acute adverse clinical effects associated with use of synthetic cathinone products range from mild to moderate neurological and cardiovascular events to case reports of cathinone-related mortality. The most commonly reported symptoms include agitation, combative behavior, tachycardia and related cardiovascular events, paranoia, confusion, hallucinations/delusions, and seizures (Mas-Morey, et al., 2012; Murphy, et al., 2012; Spiller, et al., 2011). Consistent with the tendency for these substances to induce amphetamine-like psychoses, Spiller et al. (2011) reported examples from 236 cases in which intense but rare behavioral episodes occurred following “bath salt” intoxication including “walking into a river in January to look for a friend who was not there,” and “leaving a 2-year-old daughter in the middle of a highway because she had demons” (p. 501). Patterns and consequences of use consistent with formal diagnostic criteria for substance abuse and dependence have also been reported among users (Winstock, et al., 2011).

Emergency room patients presenting with this constellation of mild to severe physiological, behavioral, and mental symptoms should be managed in a manner similar to amphetamine or cocaine toxicities and can include administration of benzodiazepines, antipsychotics, or propofol in accordance with the behavior of the patient and aggressive cooling in cases involving hyperthermia (Mas-Morey, et al., 2012; Penders, 2012; Prosser & Nelson, 2012; Spiller, et al., 2011). Controlled investigation is lacking, but reports suggest that the effects of these drugs last approximately 1–3 hours, but that users tend to repeat dosing for highs lasting a total of 8–10 hours (Penders, 2012; Winstock, et al., 2011). For a detailed flow chart to guide clinical management of intoxication symptoms, see Figure 1. At present, treatment approaches must remain dynamic and responsive to individual symptoms as they appear to the healthcare professional.

***Salvia Divinorum* (a.k.a. “Salvia”)**—The plant *Salvia divinorum* is a member of the mint family that has been used historically in ethnomedical and ceremonial practices in Oaxaca, Mexico (Ott, 1995, 1996; Siebert, 1994; Valdes, 1994) and has gained increased popularity as a recreational drug (Perron, Ahmedani, Vaughn, Glass, Abdon, & Wu, 2012; Wu, Woody, Yang, Li, & Blazer, 2011). Salvinorin A, the primary psychoactive compound in *Salvia divinorum*, is a unique hallucinogen in that it is not active at the 5-HT_{2A} serotonin receptor, the primary site of activity for classic hallucinogens such as LSD and psilocybin (Cunningham, Rothman, & Prisinzano, 2011; Prisinzano, 2005; Roth, Baner, Westkaemper, Siebert, Rice, Steinberg, et al., 2002). Although *Salvia divinorum* and salvinorin A have not been controlled at the federal level in the US, legislative bodies have enacted various levels of restriction in 34 states within the US and at least 24 nations at the time of this writing (<http://www.sagewisdom.org/legalstatus.html>). Products containing *Salvia divinorum*, often containing additional quantities of extracted salvinorin A, are typically smoked in non-traditional use (Baggott, Erowid, Erowid, Galloway, & Mendelson, 2010; Gonzalez, Riba, Bouso, Gomez-Jarabo, & Barbanoj, 2006). Although traditional use of *Salvia divinorum* involves oral consumption of a tea made from leaves, buccal absorption rather than gastrointestinal absorption may be at work with this method of administration (Siebert, 1994). There is interest in using salvinorin A and related compounds to study kappa opioid mechanisms and develop therapeutics in neurological disorders (e.g., Alzheimer’s disease),

pain, and cocaine dependence (Cunningham, Rothman, & Prisinzano, 2011; Kivell & Prisinzano, 2010; Mello & Negus, 2000; Morani, Kivell, Prisinzano, & Schenk, 2009; Sheffler & Roth, 2003; Tejeda, Shippenberg, & Henriksson, 2012).

Epidemiology—Since the 1990s use of *Salvia divinorum* has increased to point that the prevalence of lifetime use by young people is similar to traditionally recognized drugs of abuse such as cocaine. The increase in use of *Salvia divinorum* appears to have stabilized recently, with lifetime use among 12th grade students in the U.S. remaining near 6% from 2009 through 2011 (Johnston et al., 2012). Surveys suggest that many users only use the drug a few times in their lifetime (Baggott, et al., 2010; Gonzalez, et al., 2006). An interesting recent trend among users is to videotape their behaviors during an episode of use. A recent search for “salvia” on the video sharing website www.youtube.com yielded video footage of over 30,000 people, primarily adolescents and young adults, under the influence of *Salvia divinorum*.

Toxicology—Use of *Salvia divinorum* or salvinorin A is not currently detectable by standard drug urinalysis typically used clinically. However, salvinorin A has been shown to be detectable in body fluid by liquid chromatography-mass spectrometry (McDonough, et al., 2008), gas chromatography/mass spectrometry (Pichini, et al., 2005), and high performance liquid chromatography-atmospheric pressure chemical ionization (Schmidt, et al., 2005).

Pharmacology—Salvinorin A, a neoclerodan diterpene, is a nonnitrogenous kappa opioid agonist, with no other known activity across 50 other receptors, transporters, and ion channels, including the 5-HT_{2A} serotonin receptor, which is the principal site of activity of classic hallucinogens such as LSD and psilocybin (Prisinzano, 2005; Roth, et al., 2002). Studies characterized structure-activity relationships and the molecular mechanisms for salvinorin A binding to the kappa opioid receptor (Chavkin, et al., 2004; Munro, Rizzacasa, Roth, Toth, & Yan, 2005; Yan, et al., 2005). Studies in monkeys show that salvinorin A produces discriminative stimulus effects similar to other high efficacy kappa agonists (Butelman, Rus, Prisinzano, & Kreek, 2010). A kappa-like profile of antinociceptive and behavioral effects has also been demonstrated in rodents (Carlezon, et al., 2006; Fantegrossi, Kugle, Valdes, Koreeda, & Woods, 2005; McCurdy, Sufka, Smith, Warnick, & Nieto, 2006; Wang, et al., 2005; Zhang, Butelman, Schlussman, Ho, & Kreek, 2005). Salvinorin A was shown to produce several effects different from classic drug reinforcers: it elevated thresholds for intracranial stimulation (Zhang, et al., 2005), produced conditioned place aversion (Carlezon, et al., 2006), and decreased dopamine levels in the caudate putamen in mice and nucleus accumbens in rats (Carlezon, et al., 2006; Zhang, et al., 2005), although it should be noted that conditioned place preference has been shown under some conditions (Braidia, et al., 2008; Braidia, et al., 2007).

Clinical consequences—Behavioral toxicity associated with intense psychological effects is most likely adverse effect of using *Salvia divinorum*. The most frequent acute clinical consequences of *Salvia divinorum* or salvinorin A are sedation and perceptual distortions (McCurdy, et al., 2006). Case reports have noted somatic sensations such as

prickling of the skin, fever-like hot flashes, muscular tremor, and ringing in the ears (Bucheler, Gleiter, Schwoerer, & Gaertner, 2005). Human laboratory research with salvinorin A has reported disruptions in vestibular and interoceptive functioning (e.g., sensations moving in a particular direction, spinning, stretching) (Johnson, MacLean, Reissig, Prisinzano, & Griffiths, 2011; Maclean, Johnson, Reissig, Prisinzano, & Griffiths, 2012). Severe impairment of motor ability as well as disruptions in human memory recall and recognition have also been demonstrated following high doses of salvinorin A (Maclean, et al., 2012).

When the substance is inhaled via smoking or vaporization, the duration of drug action is extremely brief, with effects being reported immediately after inhalation, peak effects occurring at approximately 2 minutes after inhalation, and with definitive subjective effects dissipating at an average of approximately 20 minutes after inhalation (Johnson, et al., 2011; Maclean, et al., 2012). When the drug is administered via buccal absorption, effects are reported to begin within 5–10 minutes, followed by plateau effects lasting for approximately 1 hour, and by waning effects over an additional 1 hour (Siebert, 1994). However, in a recent laboratory experiment buccal administration of salvinorin A across a range of doses failed to yield discriminative subjective effects in human participants (Mendelson, et al., 2011).

A small percentage of users have reported persistent anxiety after *Salvia divinorum* use, however a larger percentage of users reported persisting positive psychological effects (Baggott, et al., 2010). There are two case reports of persisting psychotic-type episodes associated with *Salvia divinorum* use (Paulzen & Grunder, 2008; Singh, 2007), although both cases were complex and therefore difficult to causally attribute to the use of *Salvia divinorum*. That said, the theoretical possibility remains that exposure to *Salvia divinorum* in those predisposed to psychotic process could trigger a psychotic episode, a concern associated with use of classic serotonergic hallucinogens and cannabis (D'Souza, 2007; Johnson, Richards, & Griffiths, 2008).

Although human research suggests acute abuse liability in experienced hallucinogen users (Maclean, et al., 2012), and nonhuman data shows mixed evidence of abuse liability using the conditioned place preference procedure (Braidá, et al., 2008; Braidá, et al., 2007; Zhang, et al., 2005), addiction to *Salvia divinorum* is not commonly reported by users (Baggott, et al., 2010), consistent with users typically reporting a low number of lifetime uses (Baggott, et al., 2010; Gonzalez, et al., 2006).

Salvinorin A is associated with relatively little physiological toxicity. In controlled human laboratory studies, doses of salvinorin A that produced strong subjective effects did not result in changes in blood pressure or heart rate (Johnson, et al., 2011; Maclean, et al., 2012). In rodents, high doses of salvinorin A administered for two weeks did not result in significant changes in spleen, blood, brain, liver, kidney or bone marrow (Mowry, Mosher, & Briner, 2003). In a second experiment, high doses of salvinorin A administered acutely had no effect on ECG cardiac conduction (no effect on QT interval or PR interval), temperature, galvanic skin response, or pulse pressure. Non-human primate studies also suggest a benign toxicological profile for salvinorin A (Butelman, et al., 2007).

Emergency department reports of adverse psychiatric reactions are surprisingly rare for *Salvia divinorum* considering the prevalence of its use and intensity of subjective effects. This may, in part, relate to the very short time course for the drug (with the common inhalation route) relative to classic hallucinogens such as LSD. That is, adverse psychiatric effects may likely spontaneously resolve prior to seeking or obtaining medical care. The longer time course associated with the less common buccal administration route may render emergency medical treatment of salvinorin A adverse reactions more likely. Regardless of route, given the relatively safe physiological profiles of the drug, if an individual is experiencing an adverse psychological reaction (e.g., anxiety, panic), the treatment of choice (if logistically possible) is to provide strong interpersonal reassurance and support, similar to advice for treating adverse psychological reactions to classic hallucinogens such as LSD (O'Brien, 2006). If pharmacological intervention is judged necessary, intravenous naloxone may be used to reverse drug effects, although it should be noted that reversal will likely require a dose approximately 5 to 10 times the dose needed to reverse the reaction to a mu-opioid agonist (e.g., heroin), because naloxone has approximately 5 to 10 times the affinity for mu relative to kappa receptors (Ko, Butelman, Traynor, & Woods, 1998; Walsh, Chausmer, Strain, & Bigelow, 2008). Naloxone has been successfully and safely used to treat an accidental kappa opioid agonist poisoning in a human (Woods, 2006, personal communication). Kappa opioid antagonists have also successfully reversed salvinorin A toxicity in rhesus monkeys (Butelman, 2006, personal communication). Naloxone has a remarkably efficacious and safe profile (Jacobsen & Haines, 1997; Sporer, 1999). As with classical hallucinogens, pharmacological treatment options may also include benzodiazepines and antipsychotic agents.

Discussion

Synthetic cannabinoids, synthetic cathinones, and *Salvia divinorum* are preeminent components of a new and burgeoning “legal” drug market most popular among adolescents and young adults. Fueled by the rapid transfer of information in the Internet age, clandestine chemists are able to identify and produce what appears to be an endless chain of psychoactive drugs with pharmacological profiles that contain key features associated with drugs of abuse. These drugs are then readily substituted as undisclosed ingredients in bogus commercial products (e.g. labeled as incense, bath salts, plant food) sold in stores and over the Internet without any regulatory oversight, and often without restrictions regarding the age of the person purchasing them. Thus, youth are able to legally purchase products that contain psychoactive drugs with potency and efficacy often substantially greater than traditional drugs of abuse, that may contain additional contaminants, and for which clinicians have limited methods for detecting use and inadequate pharmacological knowledge. Worldwide sales of products over the Internet have also made enforcement of regional bans challenging for law enforcement agencies. This emerging trend in substance use clearly presents significant and unique public health and criminal justice challenges.

Due to the clandestine nature of synthetic drug production, it is often difficult to specify the psychoactive ingredients responsible for toxicity when presented in a clinical setting. Currently, the analytical methods used to identify/detect these drugs requires a high level of technological sophistication not likely available to most healthcare professionals resulting in

the need to determine a course of treatment with limited information. Given that new substances are continually being introduced, development of technologies capable of rapid, accurate detection of synthetic drugs is a significant challenge and a barrier to effective clinical management. Clinicians must learn to recognize the physiological and behavioral effects of the variety of novel drugs entering the market in order to accordingly determine a course of treatment.

In response, efforts need to be made to increase the speed at which new drugs are detected and then incorporated into scientific monitoring and discovery. This should include expanded forensic testing capabilities among public health and law enforcement agencies, enhanced communication between these entities about recognition of emerging substances, and the development of surveillance systems for monitoring Internet and social media sources of novel drug use information used by and shared among users. From the point of identification, it is essential to then accelerate the rate of scientific analyses. In the recent case of synthetic cannabinoids, it has been seven years since initial reports of use surfaced and use of these substances is only now being added to epidemiological surveys and human laboratory studies have yet to be conducted.

Moving forward, comprehensive epidemiological data will be essential for monitoring patterns of use over time as well as determining rates of use among sub-populations to inform targeted prevention efforts. While the published case reports have helped identify specific risks associated with use of these substances, little is known about the exact rate at which these events occur relative to total uses, or the role of demographic, health risk factors, past or concurrent other drug use, or effects/doses of specific substances on development of these outcomes. Systematic laboratory research is also needed to evaluate the dose effects of specific substances under controlled conditions in order to develop biological assays with defined windows of detection and to establish valid pharmacodynamic and pharmacokinetic profiles.

At this point, the trajectory of the “legal” high and synthetic drug market is difficult to assess. The adoption of these substances was rapid and far-reaching, but is now being countered by the adoption of new regulatory controls and strong public health messages communicated through various media outlets. That poison control calls in the U.S. declined for both synthetic cannabinoids and cathinones in 2012 compared with 2011 is encouraging (AAPCC, 2012a, 2012b), but use of synthetic cannabinoids remained level in 2011 and 2012 and ranked second only to cannabis in overall prevalence of use (Johnston et al., 2012). Also, the fact that specific drugs such as mephedrone and JWH-018 have been placed under regulatory control, yet continue to be detected suggests that a market for at least some of these new substances may be established independent of their legal status (Ernst et al., 2012; Winstock et al., 2010). It is also possible that the market could expand to include a number of additional classes of drugs. Several other novel drugs (e.g. tryptamines, phenethylamines, piperazines, kratom, cocaine derivatives, and ketamine derivatives), exist, but were omitted from this review due to the dearth of scientific data available.

In summary, the current novel drug market represents a dramatic shift from illicit drug markets of the past. It is imperative for the medical field to recognize this trend in drug use,

to share information regarding the emergence and consequences of new substances, and to incorporate discussion of these drugs and their risks with patients. In order to stay current, new technologies will need to be developed for detection of new drugs both in the market place and in the clinic, and this will require cooperated efforts among clinical, research, and law enforcement communities.

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Figure 1.

Clinical management of the sympathomimetic toxidrome related to synthetic cathinones consumption. The treatment is basically supportive and should consider gastric emptying and the administration of activated charcoal as a first step, unless the patient is sedated and not able to protect its airway. In this case, the airway should be protected by endotracheal intubation. Finally, if the patient is dehydrated, boluses of intravenous NaCl 0.9% 10 to 20 mL/Kg have to be considered. This Figure has been reproduced from Mas Morey et al., 2012 with permission from Sage Publishing