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REVIEW ARTICLE

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

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Abstract Despite their widespread Internet availability and use, many of the new drugs of abuse remain unfamiliar to health care providers. The herbal marijuana alternatives, like K2 or Spice, are a group of herbal blends that contain a mixture of plant matter in addition to chemical grade synthetic cannabinoids. The synthetic cathinones, commonly called "bath salts," have resulted in nationwide emergency department visits for severe agitation, sympathomimetic toxicity, and death. Kratom, a plant product derived from *Mitragyna speciosa* Korth, has opioid-like effects, and has been used for the treatment of chronic pain and amelioration of opioid-withdrawal symptoms. *Salvia divinorum* is a hallucinogen with unique pharmacology that has therapeutic potential but has been banned in many states due to concerns regarding its psychiatric effects. Methoxetamine has recently become available via the Internet and is marked as "legal ketamine." Moreover, the piperazine derivatives, a class of amphetamine-like compounds that includes BZP and TMFPP, are making a resurgence as "legal Ecstasy." These psychoactives are available via the Internet, frequently legal, and often perceived as safe by the public. Unfortunately, these drugs often have adverse effects, which range from minimal to life-threatening. Health care providers must be familiar with these important new classes of drugs. This paper discusses the background, pharmacology, clinical effects, detection, and management of synthetic cannabinoid, synthetic cathinone, methoxetamine, and piperazine exposures.

Keywords Legal highs · Drug abuse · Designer drugs · Emerging drugs · Herbal

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Introduction

The recent proliferation of unregulated psychoactive substances is unprecedented in the annals of drugs abuse. European authorities described the identification of 41 new psychoactive drugs in 2010 alone [1]. The majority of these new drugs can be characterized as synthetic cannabinoids, amphetamine-like stimulants, opioid-like substances, or hallucinogens [2]. These synthetic and naturally derived psychoactives are frequently legal to possess, easy to obtain from head shops or the Internet, and heavily marketed as producing similar effects to illegal drugs. Unfortunately, many of these substances can cause significant or life-threatening adverse effects. An urgent need exists for health care providers to be familiar with the effects of these novel psychoactives. More importantly, primary care providers and the medical toxicology community must develop rapid and agile strategies to recognize and report new "legal highs" as we encounter them. The goal of this article is to describe the pharmacology and clinical effects of several important classes of psychoactives including the herbal marijuana alternatives (HMAs), synthetic cathinones (bath salts), Kratom, *Salvia divinorum*, methoxetamine, and the piperazine derivatives.

Herbal Marijuana Alternatives

HMAs, such as *Spice* and *K2*, have been recognized as drugs of abuse in Europe since the early 2000s. *Spice*, and other brand name HMAs like *K2*, are marketed as incense and potpourri, and labeled "not for human consumption." Their actual contents or ingredients are rarely clearly labeled on the packaging, and brand names may vary widely (see Table 1). Users recognize HMAs as legal alternatives to marijuana that purportedly achieve the same clinical effects, but are not detectable by traditional marijuana screening methods [3–6]. Sold in blends that often contain more than ten herbal additives, the substrate herbs are difficult or impossible to identify.

HMAs are intentionally adulterated with synthetic cannabinoid chemical compounds. These compounds represent a small fraction of the many available synthetics designed by pharmaceutical companies and researchers exploring cannabinoid receptor-ligand binding. Since the 1960s, the pharmaceutical and research communities have been in search of cannabinoid receptor agonists with the analgesic and anti-inflammatory properties of tetrahydrocannabinol (Δ9-THC), without the psychotropic side effects [7–12]. The synthetic cannabinoids developed over this time have led to a better understanding of the cannabinoid receptors (CB_1 and CB_2) [3, 13–22]. Consequently, there are hundreds of synthetic cannabinoids that may be incorporated in HMAs with herbal constituents or abused as single-ingredient powdered mixtures [23, 24].

After European and Russian authorities banned *Spice* and other synthetic cannabinoids in 2010, *Spice* and another HMA brand name, *K2*, appeared in the USA [25–27]. In early 2011, the US Drug Enforcement Administration (DEA) gave schedule I status to several of the synthetic cannabinoids (JWH-018, JWH-073, JWH-200, CP 47-497, and CP 47-497C8 homologue) [28]. However, HMAs are still available on the Internet and in local head shops in the USA with updated marketing claiming that they contain no banned substances. The popularity of HMAs prompted the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) special investigation and report, which describes the evolution of the *Spice* phenomenon [14].

Table 1 Brand names of common HMAs [16]

Spice	Chill zone cherry	Chaos mint
K2	Chill zone mint	Chaos original
Tai fun blackberry	Chill zone original	Chaos cherry
Tai fun vanilla	Chill out cherry	Smoke
Tai fun orange	Chill out mint	Clover Spring
Exclusive original	Chill out original	Aztec thunder
Exclusive mint	Sensation vanilla	Red Merkury
Exclusive cherry	Sensation orange	Zen
Natures organic jagoda (blackberry)	Sensation blackberry	Zen ultra
Natures organic wisnia (cherry)	Sensation vanilla 2	
Natures organic truskawka (strawberry)	Sensation blackberry 2	

Because HMAs are available largely via the Internet, monitoring of the Internet community has been an important means of understanding emerging trends in their abuse [29]. The Internet's anonymity makes identifying and understanding the population of HMA users challenging [29, 30]. For example, HMA users may be adolescents, young adults, or college students experimenting with new drugs [31], or they may be adults motivated to avoid drug detection, such as military personal or those working in occupations associated with frequent drug testing [32–35].

The initial surveillance and tracking of HMAs took place in the European Union (EU) via an early warning network (Reitox), as well as an innovative Internet investigative project (Psychonaut) searching proactively for emerging patterns of drug abuse [36, 37]. The Reitox early warning system involves the 27 EU member states coordinating efforts to help identify emerging drugs of abuse. A similarly coordinated early warning network exists in the USA called the Community Epidemiology Work Group (CEWG). Established by the National Institute of Drug Abuse (NIDA), and drawing representation from major metropolitan areas, the CEWG meets semiannually, where members present their geographically unique trends in drug abuse. The CEWG identified the emerging *K2* epidemic in the Midwestern USA in 2010 [38]. By summer of 2010, a report of over 1,000 cases of synthetic cannabinoid-induced toxicity was available via the American Association of Poison Control Centers for 48 states and the District of Columbia [39]. A new database (ToxIc) shows promise in identifying emerging drugs like *K2*. Created by the American College of Medical Toxicology (ACMT), ToxIc provides a means for the toxicology community to centralize and research observations on what are frequently smaller, geographically specific patterns in emerging drugs of abuse.

As awareness of the *K2* epidemic grew, local and federal law enforcement efforts culminated in the scheduling of the most frequently identified synthetic cannabinoids present in HMAs: JWH-018, JWH-073, JWH-200, CP 47-497, and CP 47-497C8 homologue [28]. The rapid scheduling of these synthetic cannabinoids met with mixed opinions; some researchers expressed concern that "reclassification of synthetic cannabinoids in Schedule I of the Misuse of Drugs Regulations could hamper research" on the potential benefits of cannabinoids in treating a myriad of human disease processes [40].

Pharmacology/Pharmacokinetics

The pharmacologic effects of HMAs are likely to be dually derived from their herbal ingredients and intentionally

added synthetic cannabinoids. There is a paucity of ethnobotanical and pharmacologic evidence corroborating the herbs' historically referenced psychotropic effects, and it is unclear why the following herbs have been chosen for HMA inclusion: baybean, beach bean, blue lotus, dog rose/rosehip, lion's ear/tail, wild dagga, lousewort, Indian warrior, dwarf skullcap, maconha brava, blue/sacred lotus, pink lotus, white and blue water lily, marshmallow, red clover, rose, Siberian motherwort/honeyweed, vanilla, and honey [14]. There is almost no medical literature to guide clinicians about the effects or toxicity of many of these herbs. The most well known of these herbs is *Leonotis leonurus*, or wild dagga, a South African plant that has been used for its cannabis-like effects [41].

Synthetic cannabinoids can be divided into seven major structural groups: (1) naphthoylindoles (JWH-018 and JWH-073), (2) naphthylmethylindoles, (3) naphthoylpyrroles, (4) naphthylmethylindenes, (5) phenylacetylindoles (JWH-250), (6) cyclohexylphenols (CP47,497), and (7) classical cannabinoids (HU-210) [42, 43]. Several synthetic cannabinoids have been identified in HMAs, including more than ten JWH compounds [16, 19, 21, 34, 39, 44, 45]. Unlike the herbal constituents mentioned above, many synthetic cannabinoids have been rigorously evaluated. Despite their lack of structural similarity with Δ9-THC (see Fig. 1), these compounds are agonists of the cannabinoid receptors (CB_1 and CB_2), and may exert activity on other receptor families as well, including NMDA [13]. Although cannabinoid receptor research is ongoing, it is believed that CB_1 and CB_2 receptors are primarily distributed in the central nervous system (CNS; basal ganglia, cerebellum, hippocampus, and cortex) and peripheral tissue (blood cells, immune tissues, and spleen), respectively [24, 46, 47]. However, there is growing evidence to suggest that CB_2 receptors may also be present in the CNS [48]. Both are G-protein coupled receptors that respond to the endogenous ligands anandamide and noladin ether, in addition to synthetic cannabinoids and Δ9-THC [13]. Of note, the synthetic cannabinoids have a demonstrably higher binding affinity for cannabinoid receptors than Δ9-THC [27].

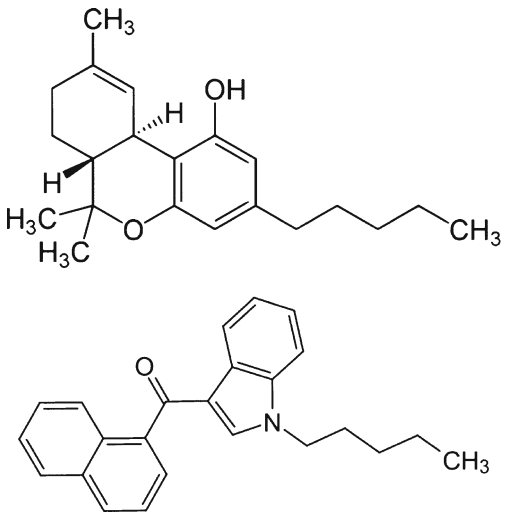

Fig. 1 Structural dissimilarity of THC (*top*) and JWH-018 (*bottom*)

CB_1 receptors have been localized to presynaptic GABAergic neurons, and CB_2 receptors on immune cells may influence the release of cytokines and cell migration [12, 49–51]. Both CB_1 receptor antagonism and CB_2 receptor agonism result in decreased vascular smooth muscle proliferation and migration via attenuation of TNF-alpha [52, 53]. In vitro murine studies have suggested a possible role for CB_2 agonists (like JWH-015) as immunosuppressive agents due to their ability to trigger apoptosis in splenic immune cells [54]. Other murine obesity models have pointed out a relationship between CB_2 receptors and obesity-associated inflammation, insulin resistance, and liver disease [55]. CB_2 receptor knockout mice experiments also suggest an association between CB_2 receptor agonism and attenuation of post-myocardial infarction ischemic-reperfusion injury [56].

HU-211 (dexanabinol)—a congener of HU-210—is an analog of Δ9-THC that has been shown to provide a neuroprotectant effect on brain damage from soman-induced seizures in rats [57]. This effect is likely due to dexanabinol's action as a noncompetitive NMDA glutamatergic antagonist [58–60]. In cultured murine hippocampal neurons, JWH-018 inhibited the excitatory postsynaptic currents in a manner consistent with CB_1 receptor agonism. When JWH-018 bound to the axonal CB_1 receptors, it inhibited glutamatergic excitatory postsynaptic currents in a concentration-dependent fashion [20].

The HMAs are typically bought as an admixture of herbs and the synthetic cannabinoids for smoking. Alternatively, users purchase the pure synthetic cannabinoid (i.e., JWH-018 powder) alone to extract and spray on any desired plant material [39].

There is essentially no human evidence that describes the absorption, distribution, metabolism, or elimination of HMAs. One case report describes a young woman with confirmed exposure to JWH-018 and JWH-073 with a reported onset of symptoms “shortly” after smoking *Spice Gold* and resolution of symptoms within 1 h [61]. While anecdotal reports support the rapid onset and brief duration of action described here, we expect that the individual synthetic cannabinoids may vary significantly in their length of effects.

Clinical Effects and Toxicity

Until recently, there have been few reports on HMA or synthetic cannabinoid clinical effects in humans [3–5, 14, 62]. To date, the clinical effects reported from HMA users exist primarily in case reports and case series [34]. Psychiatric effects predominate; anxiety, paranoia, avoidant eye

contact, agitation, delusions (paranoid and grandiose), and psychosis have been previously described [6, 63, 64]. An 18-year-old Iowa man committed suicide after smoking *K2* in the summer of 2010, prompting many of the legislative efforts to schedule the synthetic cannabinoids [65]. However, distinguishing the effects of HMAs from primary psychiatric illness may be very challenging [63].

Commonly described physical manifestations of HMA use include tachycardia, diaphoresis, conjunctival injection, and xerostomia [3, 6, 62, 63, 66]. One case report described mild hypokalemia (2.9 mEq/L) in an adolescent girl after smoking JWH-018 [62]. Seizures have been reported as a possible adverse effect by some authors; however, we have been unable to find any objective evidence or published case reports that link HMAs and seizure activity [39]. The synthetic cannabinoids have also been postulated to have serotonin-like or weak monoamine oxidase inhibitor properties [67, 68]. However, there are no published cases of serotonin syndrome in the setting of HMA use.

A single case report describes chronic synthetic cannabinoid use in a 20-year-old man who smoked 3 g of *Spice Gold* daily for 8 months; he developed tolerance and the following signs of withdrawal during his hospital admission: "inner unrest, drug craving, nocturnal nightmares, profuse sweating, nausea, tremor, headache," hypertension, and tachycardia [5]. We anticipate that a physiologic withdrawal syndrome may continue to be described in heavy, habitual users.

Detection

The myriad of herbal constituents in HMAs make detection of particular plant material difficult at best [14]. The synthetic cannabinoids identified in seized HMA samples do not appear to cross-react with the current immunoassay laboratory tests directed toward Δ9-THC. However, it has been demonstrated that the synthetic cannabinoids can be detected by gas chromatography–mass spectrophotometry (GC–MS) laboratory testing [3].

A liquid chromatography–tandem mass spectrometry (LC–MS/MS) method has been described for measuring JWH compounds, CP 47-497, and their glucuronidated and oxidized metabolites [17, 42]. Dresen et al. demonstrated the presence of synthetic cannabinoids in 57 urine samples, using LS-MS/MS. Their testing demonstrated the presence of JWH-081 as the most prevalent compound, followed by JWH-250, JWH-018, JWH-073, and JWH-015 [69]. Detection of JWH-018 in blood samples via LC–MS/MS has also been reported [42].

While parent drugs are detectable in product samples, metabolites of synthetic cannabinoids may be the only detectable compounds present in human blood or urine [70]. One report described the monohydroxylated metabolite (M1) of JWH-018 as the most abundant detectable metabolite [71]. In another study of over 500 urine samples of patients undergoing routine drug testing, metabolite-based liquid chromatography–mass spectrometry (LC–MS) screening detected JWH-018, JWH-073, and JWH-250 [72]. In a combined analysis of the "Tropical Synergy" HMA, and urine obtained from users, GC–MS analysis of plant extract confirmed the presence of JWH-018 and the C8 analogue of CP 49-497. Urine analysis via GC–MS and LC–MS demonstrated that although the parent JWH-018 compound was not detected, two glucuroconjugated and monohydroxylated metabolites were apparent [6].

There are now independent companies that advertise a commercial test for synthetic cannabinoid detection in human samples of urine or blood, as well as HMA samples. Blood testing is available for metabolites of the following compounds: AM-2201, AM-694, JWH-018, JWH-019, JWH-073, JWH-081, JWH-122, JWH-200, JWH-210, JWH-250, RCS-4, and RCS-8; urine testing is available for metabolites of the following compounds: AM-2201, JWH-018, JWH-019, JWH-073, and JWH-250 [73]. The persistence of detectable parent compounds and metabolites in urine is unknown but may range from 48 to 72 h [73].

Management

There is no pharmacologically specific antidote recognized for HMA exposures. Any patient with untoward symptoms after an HMA exposure should be directed immediately to medical care because it is difficult to know the actual contents of an HMA. Calling a Poison Control Center or seeking the nearest Emergency Department via ambulance is cautious, but prudent. Acutely, management of HMA and synthetic cannabinoid clinical effects should include supportive care and benzodiazepines for agitation and anxiety. One case report describes a 21-year-old man who required intubation for hypoventilation and "decreased level of consciousness," ultimately being discharged 24 h later [74].

Case reports vary in describing the spectrum of observed clinical effects resulting from HMA exposure and provide almost no data describing the duration of clinical effects; as such, all patients should be observed until the resolution of vital sign abnormalities, vomiting, and psychiatric derangements [74]. It is difficult to correlate the observed HMA-related effects of agitation, tachycardia, hypertension, seizure, and vomiting with the sometimes opposite effects seen with marijuana exposure.

Interestingly, there are CB_1 selective antagonists, such as SR141716, with demonstrated ability in human trials to reverse the psychotropic effects of marijuana [75]. Animal models have also demonstrated an attenuation of THC's effects by the opioid antagonist naltrexone [76]. Perhaps these antagonists will become relevant pharmaceutical

interventions as HMA and synthetic cannabinoid abuse continues to rise [77].

Summary

Rigorous study of the HMAs is extremely difficult, as the variety of herbs and synthetic cannabinoids create a moving target. Given the impressive popularity of Spice and *K2*, we do not anticipate that the criminalization of these HMAs will conclude this epidemic. Instead, we expect that other synthetic cannabinoids will be similarly packaged and marketed as the next legal marijuana.

Synthetic Cathinones ("Bath Salts")

Although "new" designer drugs containing synthetic cathinones have recently made headlines, their parent compound, cathinone, has been used recreationally for centuries. Cathinone and, to a lesser extent, its metabolite cathine are responsible for the reported amphetamine-like euphoric effects achieved by chewing the leaves and twigs of the khat plant (*Catha edulis*) [78]. This practice was first described in the medical literature in the eleventh century and continues today primarily in Yemen and several East African countries, particularly Somalia and Ethiopia [79]. In 2006, there were an estimated 10 million khat users worldwide.

The original synthetic cathinone, methcathinone, was first produced in 1928. Governing bodies grew concerned over the mental and physical consequences of khat use, prompting the first formal discussion of its potential as a public health hazard by the League of Nations in 1933. However, it was not until 1988 that cathinone was listed as a schedule I substance by the United Nations Convention on Psychotropic Substances [80]. Outbreaks were seen in both the USA and Europe in the 1990s, and it was subsequently classified as a schedule I substance in 1993 [81]. The first reports of mephedrone from Australia and multiple European countries date back to 2007 [82, 83]. Around 2009, mephedrone moved overseas to the US market, and other synthetic cathinones such as 3,4-methylenedioxypyrovalerone (MDPV) and methylone appeared soon thereafter. In the first 6 months of 2011, US poison control centers received 12 times as many calls involving "bath salt" exposure as they had for all of 2010 [84]. The number of reported analyzed drug seizures involving synthetic cathinones increased from 14 in 2009 to 290 in 2010, a 20-fold increase. Thirteen states have passed laws to control one or more synthetic cathinones, and lawmakers in several other states are considering similar legislation [85]. In September 2011, the DEA issued a notice of intent to temporarily schedule three synthetic cathinones (mephedrone, methylone, and MDPV) [86].

As many of these substances are not yet scheduled, they are being marketed to the lay public as "legal highs" or "herbal highs." Elusive packaging of synthetic cathinones is common; manufacturers often describe the drugs as bath salts, plant food, insecticides, novelty items, chicken feed additives, or research chemicals and advertise the products with names like Energy and Meow, a reference to Khat (see Table 2). Many packages also warn that contents are not for human consumption in an attempt to escape legal regulation. While synthetic cathinones are frequently called "bath salts," or "toxic bath salts," by both users and the lay press, we would discourage providers from using this imprecise terminology when identification of the individual drug is possible. The use of bath salts as a vehicle for drug delivery predates the synthetic cathinone phenomenon, with reports of bath salts as a means of concealing 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA)

Table 2 Common synthetic cathinones [81, 85, 106]

Compound	Alternative names	Product names
Cathinone		Khat
Methcathinone	Ephedrine, β-keto-methamphetamine	
Mephedrone	4MMC (4-methylmethcathinone)	Bubbles, Meow Meow, MCAT
Methedrone	4-Methoxymethcathinone, β-keto-PMMA, PMMC	
Methylone	B-keto-MDMA, MDMC	Explosion, Impact
Naphyrone	Napthylpyrovalerone	Energy-1, NRG-1
Butylone	β-keto-MBDB	
MDPV	3,4-Methylenedioxypyrovalerone	Bath salts, Ivory Wave, Vanilla Sky, Hurricane Charlie, Cloud 9, Scarface, Red Dove, White Dove, White Rush, White Lightning
4-Flouromethcathine	4-FMC, flephedrone	
3-Flouromethcathine	3-FMC	

prior to 2004 [87]. Multiple substances have been identified in more recent bath salt products, including mephedrone, MDPV, methylone, butylone, and naphyrone.

The synthetic cathinones are widely available via the Internet, but may also be sold in head shops or gas stations [88]. There is growing concern over the potential for abuse and addiction of the cathinone derivatives, given their chemical similarities to amphetamines [85]. Multiple deaths reported in by international media and the medical literature have been linked to mephedrone and bath salt products, indicating the urgent need to raise awareness and educate the public and medical communities on this topic [89–93]. However, several barriers exist to accurate data acquisition, including the variety of marketed names given to the drug, difficulties with detection, and the variability of the content and purity of acquired substance in such products [83].

Pharmacology/Pharmacokinetics

This traditional stimulant found in khat has been manipulated to create multiple synthetic cathinone analogs, in which small biochemical substitutions on the parent molecule have resulted in a new class of custom drugs with variable potency (see Table 2). Synthetic cathinones are β-ketophenethylamines, which are structurally similar to amphetamines. In fact, a single carbonyl group distinguishes methcathinone from methamphetamine, and methylone from MDMA (see Fig. 2) [94]. These small structural variations translate into several differences between the two classes of compounds. Cathinone derivatives tend to be more hydrophilic, which decreases their ability to cross the blood–brain barrier and renders them less potent than their amphetamine counterparts [94, 95]. Also, the carbonyl group makes the cathinone molecule more planar, which some authors propose could lead to cellular toxicity via insertion into DNA [94]. Cathinone, mephedrone, methcathinone, and methylone have all been shown to strongly inhibit reuptake of dopamine, serotonin, and norepinephrine [96–100]. The substances also increase presynaptic release of the same monoamines, but to a lesser extent [99].

There are limited data in the medical literature on the pharmacokinetics and pharmacodynamics of the synthetic cathinones in humans. Synthetic cathinones are most commonly sold as a white or brown powder, but capsules and tablets are also available. Multiple routes of exposure have been reported, including nasal insufflation, oral ingestion, rectal insertion, and intravenous/intramuscular injection [88, 101]. Based on user reports, typical doses of mephedrone and methylone are 100–200 mg orally, with onset of effects around 30 to 45 min and a duration of 2 to 5 h [102, 103]. MDPV seems to be more potent, causing effects 15 to 30 min after a typical oral dose of 10–15 mg. The psychoactive effects may last from 2 to 7 h [104]. Studies of mephedrone metabolism have demonstrated (1) demethylation to the primary amine, (2) reduction of the keto moiety to an alcohol, and (3) oxidation of the tolyl moiety [105]. The resulting metabolites can assist in detection of mephedrone and other synthetic cathinones.

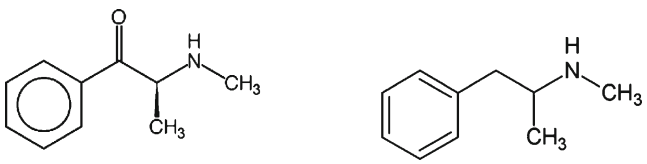

Fig. 2 Structural similarity of mephedrone (*left*) and methamphetamine (*right*)

Clinical Effects and Toxicity

Users of synthetic cathinones tend to describe a sensation of euphoria, heightened alertness, increased energy, talkativeness, and increased sexual arousal [83, 102–104]. They frequently describe the compulsion to re-dose repeatedly to titrate and/or prolong the drug's effect, with sessions lasting several hours to several days. Several recent reports describe severely aggressive and psychotic behavior demonstrated by patients who have snorted bath salts [106]. Physicians interviewed in media reports and in public service announcements recall patients' bizarre behaviors, and phenomenal physical strength, which they liken to phencyclidine intoxication. Extreme reports of self-mutilation, suicide attempts, and persistent paranoid psychosis are appearing in news reports across the USA [84, 90, 93, 107]. Users themselves describe persistent symptoms of paresthesias and mood changes for days to weeks after using both mephedrone and MDPV [102, 104].

Physical signs of synthetic cathinone intoxication are consistent with sympathomimetic toxicity and include hypertension, tachycardia, hyperthermia, dehydration, and psychomotor agitation. The most commonly reported adverse symptoms include palpitations, headache, chest pain, trismus, bruxism, tremors, insomnia, and paranoia [102, 108, 109]. There have been case reports of myocardial infarction and mephedrone-related myocarditis [110]. Multiple deaths have occurred in the setting of bath salt use, with mephedrone and MDPV identified during post-mortem toxicology [93, 111]. Like amphetamines, synthetic cathinones are considered to be capable of inducing tolerance and dependence. Thirty percent of mephedrone users reported symptoms of dependence, such as tolerance, impaired control, and craving [83, 108, 109].

As the abuse of synthetic cathinones has only recently become popular, little is known about the long-term effects of these drugs other than inferences from our knowledge of methamphetamine. However, studies have already demonstrated potential neurotoxicity. Sparago et al. demonstrated methcathinone-induced dopaminergic and serotonergic

neuron toxicity in a rodent model [112]. Similar to methamphetamine users, methcathinone users exhibited decreased dopaminergic transporter activity in basal ganglia on PET scan years after cessation of use, suggesting that they may be at risk for Parkinsonism and/or neuropsychiatric disturbances [113].

Detection

At this time, none of the synthetic cathinone derivatives are detected on routine urine ELISA-based drug screening for amphetamines; however, the cathinone derivates may cause a false positive methamphetamine screen [111]. Comprehensive analysis of serum and urine using GC–MS for synthetic cathinones has been described [95, 105]. Both GC–MS and LC–MS testing kits are available commercially for mephedrone, MDPV, and methylone [111, 114].

Management

Diagnosis of exposure, intoxication, and or toxicity can be challenging, as patients may be unable to share key historical details. The emergency and acute care physician must maintain a high index of suspicion and for these toxins when evaluating patients with signs and symptoms of sympathomimetic toxicity.

No specific antidote exists for synthetic cathinone exposure, and there is little published data on specific management strategies. Current practice is based on experience with other sympathomimetic agents, and supportive care is the mainstay of therapy. Aggressive sedation with benzodiazepines is indicated as needed for agitation, seizure, tachycardia, or hypertension. If hypertension persists, it is reasonable to treat with titratable vasodilators (i.e., nitroglycerin or sodium nitroprusside). Beta blockade should be avoided due to potential exacerbation of hypertension due to unopposed alpha-adrenergic stimulation. Significant hyperthermia may require passive or active cooling if not resolved with anxiolysis and sedation [101, 109].

All moderate to severely symptomatic patients should have an electrocardiogram, be placed on a cardiac monitor, and receive serial temperature checks. Evaluations to consider include CPK, electrolytes, renal/liver function tests, cardiac enzymes, and testing for coingestants and/or adulterants. Disposition is based on symptomatology. Asymptomatic patients with no suspected coingestants or suicidal symptoms can be considered for discharge home. Symptomatic patients should be monitored until resolution of symptoms and vital sign abnormalities. Those with persistent vital sign, neurologic, or psychiatric abnormalities should be admitted. Patients with severe hyperthermia, recurrent seizures, coma, arrhythmia, or need for intubation should be admitted to an intensive care setting [109]. In a case series of 35 patients who presented to the ED after using "bath salts," 26% were admitted to an intensive care unit, 14% to the medical floor, and 9% to the psychiatric unit [93].

Summary

Synthetic cathinones are an updated, custom version of the traditional psychostimulant found in the khat plant. These substances are packaged as other products (such as bath salts or plant food) that are "not for human consumption" in order to avoid detection and prosecution. However, they are actively being "consumed" throughout the USA and Europe with serious individual and public health consequences similar to amphetamines. Additional research is needed to better characterize each of these substances.

Kratom

As the epidemic of opioid addiction grows, opioid-tolerant individuals frequently seek methods to avert withdrawal symptoms when opioids are unavailable to them [115, 116]. Kratom, a legal plant product, has been used for centuries to treat opioid withdrawal and is accessible via the Internet without a prescription [116–119]. Derived from *Mitragyna speciosa* Korth, a Southeast Asian tree, Kratom has unusual dual properties resulting in stimulation and analgesia. Kratom was federally prohibited by Thailand in the 1940s and Malaysia in 2003 [119, 120]. Despite the US Drug Enforcement Administration listing Kratom as a drug of concern, Kratom's popularity persists on the Internet and is one of the top five legal highs in the UK [121–124].

Pharmacology/Pharmacokinetics

M. speciosa Korth is a plant made up of more than 25 alkaloids that vary in specific composition depending on the plant's geographical location [116, 119, 125–128]. Structurally similar to yohimbine, mitragynine is the most abundant of these alkaloids and is thought to be primarily responsible for Kratom's opioid-like effects [129]. However, mitragynine is structurally distinct from opiates, like morphine and codeine (see Fig. 3). Murine models suggest that mitragynine acts at supraspinal mu- and delta-opioid receptors, as well as serotonergic and noradrenergic pathways in the spinal cord [119, 130, 131]. Animal studies suggest that mitragynine may stimulate post-synaptic alpha-2 adrenergic receptors and/or block stimulation of 5-HT_{2A} receptors [132].

Kratom's popularity as a treatment for muscle pain may be attributed in part to a widely quoted study which demonstrated neuromuscular blockade at the neuromuscular

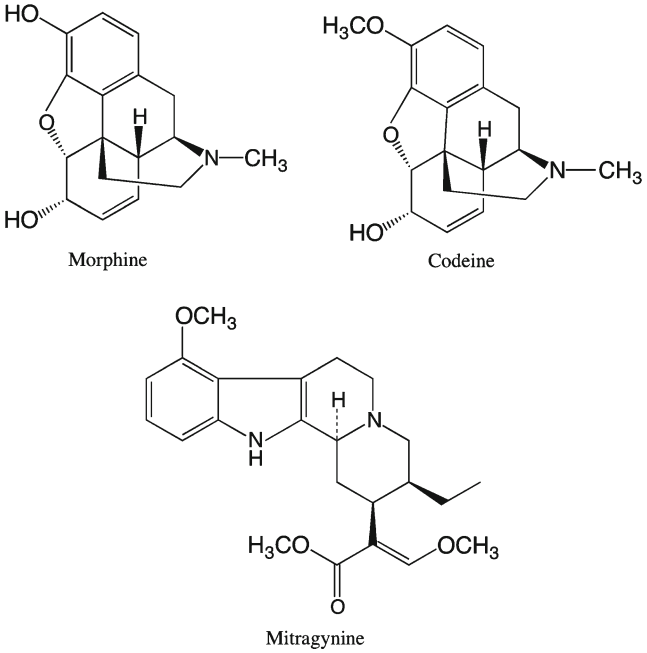

Fig. 3 Structural differences between classic opioids and the kappa-opioid receptor agonist, mitragynine

junction where rat phrenic nerve-hemi diaphragms were exposed to Kratom extract [125].

Mitragynine is approximately 13 times more potent than morphine, while 7-hydroxymitragynine (a minor component of *M. speciosa* Korth) is four times more potent than mitragynine [119, 133]. In rat models, mitragynine's time to peak plasma concentration and elimination $t_{1/2}$ were 1.26 and 3.85 h, respectively [134].

Current commercially available Kratom products are available as powder, leaves, and gum, and the drug is typically smoked or brewed into tea [135]. Reported benefits of Kratom use include analgesic, anti-inflammatory, antipyretic, antitussive, antihypertensive, local anesthetic, hypoglycemic, antidiarrheal, and antimalarial effects; other purported benefits include improving circulation, relieving muscle pain, and prolonging sexual intercourse [117, 118, 128, 136]. Kratom's cocaine-like effects at lower doses may be likened to morphine's similar effect at lower doses [137]. Effects are dose-dependent, beginning 5 to 10 min after consumption, and lasting for 1 h after exposure [138].

Clinical Effects/Toxicity

The clinical effects of Kratom are dose-dependent. At low doses, Kratom produces a stimulant effect; at higher doses, the opioid effect predominates [121]. In a cross-sectional survey of 136 Malaysian Kratom users, 88% of short-term users and 80% of long-term users (>2 years) stated that *M. speciosa* reduced their withdrawal symptoms from opioids [119].

A 32-year-old man using Kratom required intubation after his seizure did not respond to adequate benzodiazepines [139]. Thirty minutes after ingesting a Kratom/*Datura* tea mixture for chronic pain, a 64-year-old man was similarly intubated for seizure activity; mitragynine was detected in his urine [140]. From these case reports, it is not possible to infer whether Kratom caused the seizure by a pharmacologically supported mechanism or instead contributed to an opioid-induced hypoxia.

A case report of a 44-year-old man described the diagnosis of primary hypothyroidism presenting during Kratom use for chronic abdominal pain [141]. The patient experienced withdrawal symptoms from Kratom when he tried to stop using it, noting "cramping abdominal pain, sweating, and diarrhea" [141]. Subsequent lethargy and myxedema of the face responded to levothyroxine, methadone, and oxycodone treatment and cessation of Kratom abuse [141]. No causal relationship between Kratom and thyroid dysfunction has been identified yet. A withdrawal syndrome has also been described in chronic Kratom users reporting irritability, yawning, rhinorrhea, and diarrhea [138]. One contemporary case report describes a 44-year-old patient who manifested the following signs of withdrawal from Kratom: "anxiety, restlessness, tremor, sweating, and cravings for the substance" [142]. He also had a history of alcohol abuse and anxiety, and he was reportedly successfully treated for his withdrawal with a regimen of dihydrocodeine and lofexidine [142].

A case report from Germany of a 25-year-old man describes a 2-week exposure to Kratom; a subsequent liver biopsy identified drug-induced cholestatic injury without hepatocellular damage, while urine and serum analysis confirmed the presence of mitragynine [143].

In a case series from Sweden, the powdered mixture "Krypton" was implicated in nine human deaths over a 1-year time period [144]. The presence of both mitragynine and *O*-desmethyltramadol (the active metabolite of tramadol) were confirmed in postmortem blood samples, and it is believed that *O*-desmethyltramadol was intentionally added for bolstered opioid agonism [144].

Detection

Liquid chromatography–linear ion trap mass spectrometry methods permit the identification of a myriad of Kratom metabolites in rat and human urine as a means to confirm exposure to *M. speciosa* [145–149]. In another study, LC–ESI-MS analysis of 13 samples of commercial products advertising Kratom on their packaging confirmed the presence of the following compounds: mitragynine, 7-OH-mitragynine, paynantheine, speciogynine, and speciociliatine [150]. An ultra-performance liquid chromatography (UPLC) technique has also been described to identify mitragynine [151]. Recently, investigators in Japan have developed a PCR-based method to

test different plant products in order to determine whether or not they contain Kratom [135].

A case report of "Krypton" abuse demonstrated the presence of mitragynine, mitraciliatine, speciociliatine, speciogynine, and paynantheine in LC–MS/MS analysis of the patient's urine [116]. These alkaloids were found in the leaves of *M. speciosa* Korth. However, the *O*-desmethyltramadol detected is a synthetic that must have been intentionally added to the "Krypton" mixture, as it is not naturally present in Kratom [116].

Management

Given the mortality associated specifically with the brand of Kratom called "Krypton," it is prudent to seek immediate medical attention for any Kratom- or *M. speciosa*-associated toxicity. The protean blends of herbal products, and potential for contamination with synthetic chemicals, make the risk for opioid-related death a real and unpredictable possibility. Airway management and opioid antagonism with parenteral naloxone should be considered if the Kratom exposure results in hypoventilation. Toxin-induced seizures resulting from synthetic opioids like tramadol may not respond to naloxone; therefore, airway protection and titration of benzodiazepines are indicated. Treatment of Kratom withdrawal presenting clinically similar to opioid withdrawal may respond to supportive care as well as opioid-replacement therapy.

Summary

Kratom is being used by patients with chronic pain as a means to prevent and treat opioid withdrawal symptoms. The primary psychoactive component, mitragynine, is more than an order of magnitude more potent than morphine. Given the known withdrawal syndrome associated with this compound, urgent study is required to elucidate its abuse potential. Simultaneously, the therapeutic potential of Kratom in treating opioid addiction deserves further study.

S. divinorum

S. divinorum, an herb in the mint family that is native to Mexico, has been used for centuries for its mind-altering effects. The plant was initially incorporated in religious rituals and herbal healing by the Mazatec Indians, who would chew its leaves or brew them into tea to facilitate spiritual encounters [152]. Of the known *Salvia* species, only *S. divinorum* is known to contain salvinorin A, the component responsible for its hallucinogenic properties [153, 154].

The past decade has seen a surge in recreational use of this drug predominantly among teens and young adults across the USA, Europe, and Japan. In 2008, the US Drug Enforcement Administration (DEA) reported that five times as many specimens presented from court cases or drug seizures were identified as *S. divinorum* than the previous year [155]. In the same year, a published DEA report estimated that nationally 1.8 million people have used *S. divinorum* in their lifetime, with a disproportionate amount of users being young adults and adolescents [156]. The increased interest is likely multifactorial, with its current legal status, ease of access, lack of detection by traditional drug screens, perceived safety, and unique effect profile all playing a role [121]. Also known as "diviner's sage," "mystic sage," "magic mint," "Sally D," "Maria pastora," and "Purple Sticky," salvia is widely available via the Internet or local "head shops" [121, 153]. It is sold in prepackaged aliquots of crushed plant leaves or salvinorin A extract that can be chewed, swallowed, or (more commonly) smoked [153].

The legal status of *S. divinorum* is currently in flux. Although not officially scheduled by the US DEA, it has been labeled a "drug of concern" by the organization in 2004. Both the plant and salvinorin A are illegal to possess or distribute in several US states [156]. On the international regulatory scene, the drug is considered a controlled substance in multiple European countries, Australia, and Japan, but is not listed on United Nations and Drug Conventions Schedule as of yet [153]. Recently, media attention has focused on *S. divinorum*, when singer/actress Miley Cyrus was photographed smoking *S. divinorum* [157]. Additionally, the alleged murderer in the 2011 Tucson, Arizona shooting, Jared Lee Loughner, has been described as a long-term *S. divinorum* user [158].

Pharmacology/Pharmacokinetics

Salvinorin A is a psychotropic diterpene responsible for the hallucinogen effects of *S. divinorum*. Unlike other hallucinogens that create similar effects—like dimethyltryptamine (DMT) or psilocybin—salvinorin A does not display any proserotonergic activity and does not bind the $5HT_{2A}$ receptor [159]. Instead, salvinorin A exerts its action as a highly selective kappa opioid receptor (KOR). Stimulation of KORs results in hallucinations, diuresis, and spinal analgesia, but does not cause respiratory depression. The effects of salvinorin A are consistent with those of other KOR receptor agonists, including sedation, analgesia, inhibition of GI effects, aversion, and depression [160–164]. The role of the KOR is being investigated in the pathogenesis of mental illness, including depression and schizophrenia. The highly selective nature of salvinorin A makes it a useful probe for psychiatric research [165]. Other indirect actions may be mitigated via cannabinoid receptors, as well as dopaminergic and noradrenergic stimulation [164, 166, 167].

S. divinorum and salvinorin A are typically administered via chewing (buccal) or smoking (pulmonary) routes; the

duration and onset of effect varies with route of administration. After buccal exposure to either extract or leaf form, psychoactive effects occur within seconds to minutes, and may persist for up to 1 h [168]. Inhalation (of either vaporized salvinorin A extract or smoked dried leaves) causes hallucinations within seconds, which may last up to 20 to 30 min [168]. Two hundred micrograms of salvinorin A has been described as the threshold dose for hallucinations after inhalation, while doses of 10 mg failed to produce hallucinations after ingestion [168]. The intravenous administration of salvinorin A is not described in humans [169].

Ingestion of salvinorin A does not produce hallucinogenic effects, suggesting significant first-pass metabolism or enzymatic deactivation [168]. Salvinorin A is degraded by several cytochrome oxidase isoenzymes, including CYP 2D6, CYP1A1, CYP2C18, and CYP2E1 [170]. One ex vivo study demonstrated that salvinorin A is hydrolyzed to an inactive metabolite, salvinorin B by blood esterases [171]. However, an animal model further showed that salvinorin B is rapidly cleared in vivo and never reached detectable levels after intravenous injection of salvinorin A [169]. In one primate study, the elimination half-life of salvinorin A was 56.6±24.8 min after intravenous administration. The elimination half-life varied with gender and was significantly longer in the females [169]. In a radiolabeled study of salvinorin A uptake, high concentrations were found in the cerebellum, as well as the striatal visual cortex.

A rigorous and comprehensive review of *S. divinorum* pharmacology and pharmacokinetics has recently been published [172].

Clinical Effects and Toxicity

Typical doses of *S. divinorum* are difficult to determine due to the lack of information provided by manufacturers. *S. divinorum* is marketed in various strengths (5X–80X) which reportedly correlate with salvinorin A concentration; however, there is no reliable corresponding dose information included on the packaging. Users will typically inhale *S. divinorum* smoke from a pipe and hold it in their lungs for 10–30 s, similar to smoking marijuana; they may repeat this maneuver several times [154]. In an average session, users smoke an estimated 0.25–0.75 g of purchased material [153]. In a double bind, placebo-controlled trial in healthy humans, salvinorin A was administered in doses of 0.375 to 21 μg/kg with observed hallucinogenic effect, but no significant change in blood pressure or heart rate [173].

A rapid effect with short duration is characteristic of salvia with reported onset in 5–10 min (buccal absorption) or 30 s (inhalation). The user's peak effect experience typically lasts 15–20 min [154, 173]. Users report depth or intensity of experience is proportional to labeled concentration [152]. Users boast a "unique" intense high that some describe as reminiscent meditation/trance or intoxication with lysergic acid diethylamide (LSD), ketamine, or cannabis [174]. This includes hallucinations; distortions of visual, body image, or environmental perception; and accentuation of actual sensations. Some users describe synesthesia (i.e., hearing colors or smelling sounds) while others endorse an "out of body experience" [121, 152, 154]. Persistent effects (lasting >24 h) including "antidepressant-like effects" have been described [154].

Documented adverse effects include an intense anxiety reaction during peak effect, followed by milder persistent symptoms. During the acute intoxication phase, some users describe dysphoria and confusion with a frightening sense of a "fractured reality" and temporary language impairment [152, 175]. A "hangover" effect is often noted after peak effect wears off, including headache and drowsiness for several hours post-use [152]. One case report describes persistent psychosis in a previously healthy 21-year-old patient, suggesting that the drug may exacerbate psychiatric symptoms in those who are predisposed [176].

No characteristic physical findings have been reported in *S. divinorum* via intoxication. Of users who sought medical treatment, there were occasional reports of tachycardia and hypertension, but vital signs were largely normal in isolated exposure [173, 177]. However, the substance is frequently co-ingested with other hallucinogens and/or alcohol, which seems to increase risk of neuropsychiatric and cardiovascular toxicity [177].

The unique nature of this kappa opiate receptor system suggests potential medicinal benefits for *S. divinorum*, many of which are currently being explored. Salvinorin A has showed antidepressant and, to a lesser degree, anxiolytic-like properties in a rodent model [166]. The postulated anxiolytic effect is particularly interesting given the anxiety some users experience while intoxicated. Further studies delineating dose–response relationships may better explain this effect. Salvinorin A has also been shown to have in vivo anti-inflammatory effects in a mouse model and analgesic properties as well [178]. The compound has also been implicated as a modulator of the dopaminergic reward pathway, suggesting a potential role in addiction treatment [172].

As with all drugs of abuse, potential for dependence is a concern. Currently, there are no data to identify abuse liability in *S. divinorum* users. Of 500 *S. divinorum* users surveyed, less than 1% reported feelings of addiction or dependence [174].

Detection

High-performance liquid chromatography (HPLC) and LC–MS protocols have been applied to the quantitative analysis of salvinorin A and B in plant matter and in ex vivo animal studies. One study demonstrated the feasibility of quantifying

salvinorin A in spiked samples of primate blood, urine, and CSF. Gas chromatography–mass spectrometry (GC–MS) has been used to identify salvinorin A in the urine and saliva of two volunteers who smoked *S. divinorum* [179].

Management

A paucity of data exists on medical management of *S. divinorum* exposures, mainly due to the infrequency with which users present for medical treatment. This may be due to lack of reporting or recognition by emergency care providers, polysubstance ingestion masking symptoms, the drug's short effect, or the rare occurrence of clinically significant adverse effects.

No known antidote exists for *S. divinorum* intoxication. Some question the utility of naloxone for reversing *Salvia*-induced neuropsychiatric effects; however, no data exists on its effectiveness. Presentation for medical care for isolated *S. divinorum* exposure seems uncommon, and users are more likely to present in the context of polysubstance ingestion or trauma as a result of impaired judgment. Supportive care as dictated by clinical presentation is prudent, including sedation with benzodiazepines for severe agitation.

Summary

S. divinorum is an herbal product that is typically smoked or chewed to produce a high similar to more traditional hallucinogens like DMT or psilocybin. The primary psychoactive component found in *S. divinorum* is salvinorin A, a potent KOR agonist. Users typically report brief, but intense, and often frightening hallucinations. Aversion and dysphoria often occur. There are little data to describe potential morbidity or abuse liability associated with *S. divinorum*. Further research is needed to elucidate both the consequences of *S. divinorum* use, as well as the therapeutic potential of salvinorin A.

Methoxetamine

The recreational use of methoxetamine, a ketamine analog, has been recently reported by drug monitoring systems. A paucity of medical literature exists on this substance as of yet; much of the available information is derived from media coverage, distributors, and online user reporting. The drug first appeared in 2010 and is widely marketed via the internet as a research chemical by several online head shops [1, 180]. The UK seems to be the primary target market; however, most suppliers offer international distribution as well.

We anticipate the continued development and marketing of "legal" ketamine and phencyclidine derivatives. Already a "legal" phencyclidine derivative, 4-methoxyphencyclidine is available; however, no medical literature describes its use or toxicity.

Pharmacology/Pharmacokinetics

According to several online chemical manufacturers' websites, methoxetamine (MXE or MKET) is a synthetic analog of the arylcyclohexylamine compound ketamine. This new drug differs from ketamine by a 3-methoxy group in place of the 2-chloro group on the phenyl ring, and an *n*-ethyl group substituted for the *n*-methyl group on the amine portion of the molecule (see Fig. 4) [181, 182]. Although no formal studies have demonstrated the drug's mechanism of action, methoxetamine is likely to share ketamine's mechanism of action, through *N*-methyl-D-aspartate (NMDA) receptor antagonism and inhibition of dopamine reuptake.

Methoxetamine can be ingested orally, inserted rectally, insufflated, or injected intramuscularly. Typical doses range from 10 to 15 mg, with users reporting effects beginning in 10 min that last 1 to 2 h. Compulsive re-dosing has been described [180].

Clinical Effects and Toxicity

Users boast euphoria, perceptual distortions, and hallucinations similar to ketamine, in addition to an "opiate-like effect" [183, 184]. Unpleasant reactions include severe nausea, vomiting, diarrhea, paranoia, and anxiety [185]. Users have also described respiratory depression, antidepressant effects, and amelioration of phantom limb pain [183, 186].

Tachycardia and rotatory nystagmus have been observed [187]; however, the other adverse effects associated with ketamine, including hypertension, laryngospasm, and pulmonary edema have not been reported in methoxetamine users.

Detection and Management

The diagnosis of methoxetamine intoxication is based on patient history and presentation. Likewise, no specific management recommendations exist. However, it would be reasonable to treat intoxicated patients with a similar strategy used in those patients with ketamine or phencyclidine

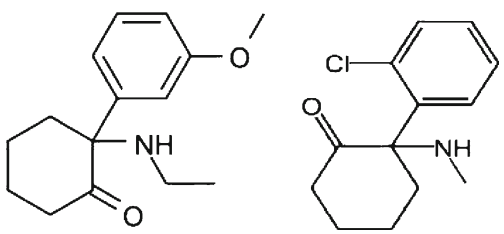

Fig. 4 Structural similarity of methoxetamine (*left*) and ketamine (*right*)

exposure: aggressive supportive care with benzodiazepines, anti-emetics, intravenous fluids, and respiratory support as needed.

Summary

There is a paucity of reliable information regarding the new ketamine analog, methoxetamine. It appears to have similar clinical effects to its parent drug. With unregulated distribution as a research chemical, it will inevitably gain popularity as another "legal high." Formal investigations are needed to better understand its pharmacology, epidemiology, and complications of use.

Piperazine Derivatives

Piperazine was originally developed as an antihelminthic that was recognized for its amphetamine-like effects. The piperazine derivatives are a popular class of stimulants often marketed as "party pills" or "legal Ecstasy." The most well known member of this class of recreational drugs is 1-benzylpiperazine (BZP or A2), but many congeners exist, including TMFPP and mCPP (see Table 3). There are many trade names for the piperazine derivative blends; some of the most common include "Benzo Fury," "MDAI," "Head rush," "XXX Strong as Hell," and "Exotic Super Strong."

BZP was given Schedule I status in 2004; however, the number of BZP exhibits submitted to US forensic laboratories grew from 437 in 2007 to 13,822 in 2009 [188]. In a 2010 survey of clubgoers in the UK, 26% had used BZP previously [189]. The other piperazine derivatives are still legal to possess and use.

Pharmacology/Pharmacokinetics

Due to the consideration of BZP as an antidepressant, pharmacologic data on this piperazine are available. BZP has central serotonergic effects caused by inhibition of serotonin reuptake and receptor agonism [190]. BZP also causes serotonin transporter inhibition. Additional in vitro studies have demonstrated that TMFPP acts on the serotonin transporter (SERT) to release endogenous stores of serotonin from neurons, in a manner similar to MDMA and other amphetamines.

Table 3 Common piperazines and chemical names

Abbreviated name	Chemical name
BZP	1-Benzylpiperazine
CPP	1-(3-Chlorphenyl)piperazine
MBZP	1-Methyl-4-benzylpiperazine
MEBP	*N*-(3-methylbenzyl)piperazine
MeOPP	1-(2-Methoxy-phenyl)piperazine
MeP	1-Methyl-3-phenylpiperazine
TMFPP	1-(3-Trifluoromethylphenyl)piperazine

The piperazine derivatives are sold as pills or powders that frequently contain blends of two to four chemicals [191]. A typical dose of BZP is 75 to 150 mg, and the resultant effect lasts 6 to 8 h. The onset of BZP effect may be more than 2 h after ingestion; many users subsequently take multiple doses before the onset of effect [192]. BZP undergoes little metabolism and is mostly excreted unchanged. In contrast, TMFPP is extensively metabolized by CYP 2D6, undergoing hydroxylation, sulfation, or glucuronidation, with partial *n*-acetylation in Phase II [193]. Several of the piperazines inhibit cytochrome oxidase isoenzymes, creating the potential for medication drug interactions [194].

Clinical Effects and Toxicity

The effects of the piperazine derivatives may be indistinguishable from those of the amphetamines, with BZP exhibiting one-tenth the potency of dextroamphetamine clinically. In low doses, piperazine derivatives cause stimulant effects, while hallucinogenic effects predominate at higher doses [192, 195]. The MDMA-like effect of the piperazines is usually achieved by mixing BZP and TMFPP.

In a prospective evaluation of 80 emergency department patient encounters involving piperazine derivatives, the most commonly reported symptoms were palpitations, anxiety, headache, and vomiting. Sinus tachycardia was common, and 32% of patients had documented QT prolongation. Seizures occurred in 14 patients, with a range of 30 min to 8 h after exposure. One patient was found to have significant hyponatremia (118 mmol/L) [196].

Detection

In one analysis of the chemical composition of "legal highs" purchased on the Internet, the authors obtained several piperazine-containing products. Several blends were found, combining BZP and TMFPP, or MBZP and TMFPP, among others. However, the authors noted that substitutions of individual piperazine derivatives frequently occurred, despite consistent packaging [197].

In spiked specimens, BZP has been variably detected on the amphetamine screen of commercial "drugs of abuse" ELISA assays. Both GC/MS and GC/NPD (nitrogen phosphorus detector) have been used to correctly identify BZP in spiked specimens [198]. With each methodology, different piperazines demonstrated similar retention times, which may facilitate identification of new congeners. HPLC with diode-array UV detection (DAD) and LC–MS have been

used together to differentiate individual piperazine isomers in a series of post-mortem cases [199].

Management

The management of the sympathomimetic toxicity associated with the piperazines parallels the management of the synthetic cathinones. Benzodiazepines, intravenous fluids, and aggressive cooling measures may be required. Seizures and agitation may be treated with benzodiazepines; seizures have been reported up to 8 h after piperazine derivative use; a prolonged period of observation may be warranted in symptomatic patients [200]. Serial electrocardiograms may be used to evaluate QT prolongation associated with piperazine use; however, no cases of torsades de pointes have been reported in association with piperazines.

Summary

While BZP was scheduled in 2004, law enforcement data suggest a resurgence in its popularity, as well as the rise of other piperazine derivatives. The possibility of severe sympathomimetic toxicity exists when these "legal" MDMA alternatives are used, particularly in combination with other piperazine derivatives or stimulants. Clinicians must consider piperazine toxicity in recreational drug users with sympathomimetic symptoms of unclear etiology.

Discussion

The ultra-rapid proliferation of "herbal" and "legal" highs has outpaced traditional surveillance and regulatory mechanisms. Once a particular product is scheduled, another similar compound is marketed in its place as the "new" legal alternative. Traditional toxicologic surveillance systems may lag in the detection of these drugs, as clinicians are frequently unaware of these novel drugs, classification is made challenging by a variety of product names and contents, and detection during drug screening is often impossible in the clinical setting. Typically, little is known about the clinical effects, potential toxicity, and abuse potential of these products [121].

Each of the drugs mentioned in this article is currently advertised as legal or were marketed as such until they were scheduled. Other factors that make them appealing to end-users include availability, price, and sought-after effect. These products are often described as "herbal" or "natural," further imbuing them with an aura of safety for some consumers [201]. While these legal highs were most commonly found at raves or clubs in years past, the explosion of Internet stores has made drugs available to anyone with access to the Internet, a credit card, and a mailbox.

The at-risk demographics are difficult to identify, as this "virtual" community of drug users is generally discovered only when adverse effects compel individuals to seek care from emergency departments or poison control centers. Innovative drug use by adolescents using the Internet has been previously identified [202], while adults may be motivated to seek out recreational drugs that are not detectable by standard methods. The difficulties with detecting many of the products used as "legal highs" can be particularly appealing to athletes, military personnel, and those with workplace drug testing. In the bath salt series, the ages of patients ranged from 20 to 55, with a median of 28 years [93].

As health care providers and law enforcement personnel struggle to respond to the rapidly changing legal high milieu, we can find opportunities to improve on our current standard. We should familiarize ourselves with the inventory of online and local head shops, and obtain detailed histories from adolescents and adults about their recreational drug use. We should recognize the limitations of detection for these products, and evaluate case reports and prospective studies on strong qualitative methodology when analytical data cannot be obtained. Simultaneously, we need to develop clinically relevant assays for this new drug landscape. We should disseminate information about these products in the medical literature and the lay media, as we strive to educate patients about the potential dangers of "legal highs."

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