Resident Journal Review – Synthetic Cathinones ("Bath Salts") and Herbal Marijuana Alternatives

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This Resident Journal Review focuses on two popular designer drugs that have made their way into the media as well as our emergency departments: synthetic cathinones, also known as "bath salts," and herbal marijuana alternatives. Due to the relative novelty of these drugs, not much literature or research exists to help ED physicians manage patients who come in with these acute intoxications. The pharmacology, clinical symptoms and management options, as well as a few case reports, will be discussed in this review.

Beyond THC: the new generation of cannabinoid designer drugs. Fattore L, Fratta W. *Frontiers in Behavioral Neuroscience*. 2011; 5:60.

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. Rosenbaum CD, Carreiro SP, Babu KM. *Journal of Medical Toxicology*. 2012; 8:15–32.

The toxicology of bath salts: A review of synthetic cathinones. Prosser JM and Nelson LS. *Journal of Medical Toxicology*. 2012; Mar; 8(1):33-42.

Herbal Marijuana Alternatives

Herbal Marijuana Alternatives (HMAs) such as K2 or Spice are sold as alternatives to marijuana that provide similar clinical effects but are not detectable by the traditional marijuana screening methods. They are basically blends of herbs adulterated with synthetic cannabinoid compounds. These synthetic compounds were initially designed by pharmaceutical companies when searching for cannabinoid receptor agonists with the same analgesic and anti-inflammatory effects of tetrahydrocannabinol (THC), without the psychotropic effects. HMAs are typically sold on the internet or in head shops as incense products, bath products, air fresheners or meditation potpourri and are sold under such names as *Spice, Spice Gold, Spice Diamond, K2, Silver, Aroma, Arctic Spice, Genie, Scene* and *Dream*. They are most commonly smoked, but they can also be infused or inhaled. Although these products first emerged on the internet and in specialty shops beginning as early as 2004, it was only in 2008 that synthetic cannabinoids were officially identified as the active ingredients in "Spice," a compound which had been marketed as an herbal blend. In early 2009, several European countries announced that any compounds containing these substances would fall under the Narcotics Law, making it illegal for them to be sold online and in head shops. That same year, the United Kingdom (UK) amended the Drugs Act of 1971 to list synthetic cannabinoids as controlled substances. However, rather than deterring sale and use of these substances, the ban only spurred development of new synthetic cannabinoid products, such as JWH-073, JWH-019, and JWH-250, among others. In March 2011, the United States Drug Enforcement Administration (DEA) ordered a temporary ban on five synthetic cannabinoids, including JWH-018, JWH-073, JWH-200, CP-47,497 and CP 47,497-C8.

The pharmacological effects of HMAs are likely from both the herbal ingredients and the added synthetic cannabinoids, although there is not much evidence or literature regarding the psychotropic effects of these herbs. Commonly used herbs in the HMAs include baybean, beach bean, blue lotus, dog rose/rosehip, lion's ear/tail, wild dagger, etc. Other substances such as synthetic opioids, monoamine oxidase inhibitors, and oleamide, a fatty acid derivative with cannabinoid-like activity, have also been isolated in many Spice products. The synthetic psychoactive compounds found in many HMA products were initially foreign to most forensic laboratories and presented a challenge to identification and referencing of these materials. Detection of these drugs is further hindered by the variable, unpredictable makeup of each product, particularly as the products are modified in response to ever-changing legal restrictions.

The synthetic cannabinoids are not structurally similar to THC but they are agonists of the cannabinoid receptors (CB1 and CB2) and may even have some effect on other receptors as well including NMDA. It is thought that the euphoric effects of the drug are due to its agonist properties at the CB1 receptor. Though in vitro studies indicate that JWH-018 acts as a full agonist at the receptor, THC is a partial agonist. Furthermore, when compared to THC, JWH-018 has a more than fourfold higher affinity for the CB1 receptor and a 10-fold higher affinity to the CB2 receptor.

Due to the lack of medical literature and research regarding the HMAs, the clinical effects are primarily known from case reports and case series. In addition to the extensive assortment of ingredients found in synthetic cannabinoid products such as Spice, there is also a wide variation in the quantity of substances present, leading to a significant incidence of accidental overdoses requiring hospitalization. Psychiatric effects that have been reported include anxiety, paranoia, avoiding eye contact, agitation, delusions, and psychosis. Common side effects of HMA include tachycardia, diaphoresis, conjunctival injection, and dry mouth. Nonetheless, the desired effects of Spice blends are frequently described as euphoric. Anxiety is one of the main unwanted side effects of acute intoxication, while severe anxiety and depression have been reported during withdrawal. Interestingly, Spice and similar products do not contain cannabidiol, a component of cannabis which antagonizes CB1 and CB2 receptors and is thought to produce anxiolysis. Although there are limited data, several deaths that occurred after taking synthetic cannabinoid products, particularly K2, have been attributed to suicide and coronary ischemic events.

The synthetic cannabinoids are not detectable by current immunoassay lab tests for THC but are detectable by gas chromatography-mass spectrophotometry (GC-MS) lab testing. When product samples are obtained, the parent synthetic cannabinoid may be detected using GC-MS lab testing. However, the metabolites of the synthetic cannabinoids may be the only detectable compounds present in human blood or urine. These are detected with metabolite-based liquid chromatography-mass

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spectrometry (LC-MS) lab testing. Currently, commercial testing for synthetic cannabinoids in human samples of blood and urine, as well as HMA samples, is available from some commercial labs.

Any patient with unfavorable symptoms after an HMA exposure should be directed to an emergency room via ambulance as it is difficult to ascertain the exact drugs involved in an HMA exposure. A Regional Poison Control Center should be consulted. Acute management consists of supportive care with the use of benzodiazepines, if needed, for the control of agitation and anxiety. In general, all patients should be observed until the resolution of abnormal vital signs, vomiting, and psychiatric symptoms. It is important to note that the common symptoms described with HMAs such as agitation and tachycardia are not typical of those seen with marijuana exposure, making the diagnosis more difficult. Although there is no antidote for HMA exposure, there are agents being studied. CB1 antagonists, such as SR141716, have been found that may reverse the psychotropic effects of marijuana. Animal models have also shown that naltrexone may attenuate THC's effects. These agents may become more relevant if the use of HMAs and synthetic cannabinoids continue to rise.

Synthetic Cathinones ("Bath Salts")

Cathinones derived from the khat plant (Catha edulis) have been used recreationally for centuries. Chewing the leaves and twigs of the plant produces amphetamine-like euphoric effects. In 2006, there were 10 million khat users worldwide. The list of synthetic cathinones is long: butylone, dimethylcathinone, ethcathinone, ethylone, 3- and 4- flouromethcathinone, mephedrone, methedrone, methlenedioxypyrovalerone (MDPV), methylone and pyrovalerone, among others. Bupropion is the only cathinone derivative that has a medical indication in the U.S. and Europe. The first synthetic cathinone, methcathinone, was produced in 1928. Methcathinone was previously used in Russia as an antidepressant, also known as "Cat" and "Jeff" when used recreationally. The United Nations Convention listed cathinones as a schedule 1 substance in 1988 and the United States did so in 1993. Mephedrone, another type of synthetic cathinone, came from Europe to the U.S. in 2009. U.S. poison control centers received 12 times as many calls involving "bath salt" exposure in the first six months of 2011 than in all of 2010. The number of seizures from synthetic cathinones increased from 14 in 2009 to 290 in 2010. In September 2011, the DEA scheduled three synthetic cathinones as schedule one (mephedrone, methylone, and MDPV). Manufacturers sell the drugs as bath salts, plant food, insecticides, chicken feed additives, or research chemicals with names like Energy and Meow. They also label them as "not for human consumption" to avoid legal regulation and prosecution. The synthetic cathinones can be found on the internet, in smoke shops, and gas stations. Multiple deaths related to bath salts exposure have been reported internationally and in the medical literature, raising concerns as the drug becomes more popular in the U.S. Synthetic cathinones are usually sold as a white or brown powder, but capsules and tablets are also available.

The method of ingestion varies, but synthetic cathinones are most commonly nasally inhaled or ingested. Rectal administration (known as "booty bombing" or "keystering"), gingival delivery, inhalation and intramuscular or intravenous injection have all been reported. "Bombing" is wrapping powder in cigarette paper and swallowing it. "Keying" is dipping a key into powder and inhaling it. Synthetic cathinones are mostly excreted via the urine and can be measured via gas or liquid chromatography-mass spectrometry in the blood, urine and stomach contents. They can also be analyzed in hair.

There are limited data on pharmacokinetics and pharmacodynamics of synthetic cathinones. The cathinone stimulant from the khat plant has been manipulated with biochemical substitutions creating a new class of drugs with variable potency. These synthetic cathinones are beta ketophenethylamines, which are structurally similar to amphetamines. Cathinone derivatives, however, tend to be more hydrophilic, which decreases their ability to cross the blood-brain barrier. They have been shown to inhibit the reuptake of dopamine, serotonin, and norepinephrine. Based on animal models, amphetamine derivatives increase synaptic concentrations of biogenic amines (norepinephrine, dopamine, and serotonin) by two primary mechanisms. The first is by inhibiting monoamine uptake transporters. The second is by causing the release of neurotransmitters from intracellular stores via changing the vesicular pH or inhibiting the vesicular monoamine transport (VMAT2) receptor. The mechanism of different synthetic cathinones varies. Methylone acts less on VMAT2 receptors compared to other amphetamine derivatives. It is a competitive inhibitor of norepinephrine reuptake but a noncompetitive inhibitor of dopamine and serotonin receptors. Mephedrone causes a greater increase in brain dopamine concentration and was noted to have a faster return to baseline level of neurotransmitters compared to MDMA. Pyrovalerone inhibits norepinephrine and dopamine reuptake, but has little effect on serotonin uptake.

The symptoms reported by users include euphoria, alertness, energy, talkativeness, increased sexual arousal, and the compulsion to re-dose frequently. Some case reports describe extremely aggressive and psychotic behavior with increased physical strength, as sometimes described in PCP intoxication. The clinical effects of synthetic cathinone intoxication are consistent with sympathomimetic toxicity and include hypertension, tachycardia, hyperthermia, dehydration, and psychomotor agitation. The patients may also report palpitations, headache, chest pain, trismus, bruxism, tremors, insomnia, and paranoia. Although much can be drawn from the structural and chemical similarities between synthetic cathinones and amphetamines, continued studies are needed to understand the particular properties including the long-term effects of synthetic cathinones.

Currently, routine urine drug screening for amphetamines is not able to detect synthetic cathinones, although they may cause false positive methamphetamine screens. However, both GC-MS and LC-MS testing kits are commercially available for some synthetic cathinones including mephedrone, MDPV, and methylone. The synthetic cathinones are mostly excreted via the urine, but can be measured in the blood, hair, urine and stomach contents.

Supportive care is the mainstay of therapy based on management of other sympathomimetic conditions. Aggressive sedation with benzodiazepines is indicated for agitation, seizures, tachycardia, and hypertension. Extreme hypertension that persists despite

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benzodiazepines may be treated with titratable vasodilators. Beta blockers should be avoided due to the potential to cause unopposed alpha-adrenergic stimulation, worsening the hypertension. Significant hyperthermia may require passive or active cooling. All moderately to severe symptomatic patients should have an electrocardiogram (ECG), be placed on a cardiac monitor, and receive serial temperature checks. Lab studies including electrolytes, renal and liver function tests, cardiac markers and creatine kinase should be considered, as should testing for coingestants or adulterants. Asymptomatic patients with no other suspected coingestions or psychiatric symptoms generally may be discharged. In a case series of 35 patients who presented to the ED after using bath salts, 26% were admitted to an intensive care unit.

Several Case Reports highlighting the dangers of these drugs…

Hyperthermia and Multiorgan Failure After Abuse of "Bath Salts" Containing 3,4-Methylenedioxypyrovalerone. Borek HA, Holstege CP. *Ann Emerg Med.* 2012 Mar 2.

This toxicology case report presents a 25-year old man who after injecting bath salts was found by police running wildly, acting combatively, and foaming at the mouth. His vitals in the ED were significant for a heart rate of 175 bpm and a temperature of 106.5 degrees rectally. On physical exam, he had mydriasis, rightward deviation of the eyes, and extreme warmth. He was agitated until he was intubated with etomidate and succinylcholine. Over the following hour his temperature and pulse normalized with ice packs and cooling blankets. His labs were significant for the following: white blood cell count 17,000/mm3, potassium 5.1 mEq/L, serum bicarbonate 14 mEq/L, creatinine 2.88 mg/dL, glucose 45 mg/dL, troponin 3.24 ng/mL, and lactate 7 mg/dL. The urine drug screen was positive for benzodiazepines, which had been administered 90 minutes prior to collection. ECG, computed tomography of his head and cerebrospinal fluid were all normal.

During the next 2 days the patient developed renal failure, fulminant hepatic failure, disseminated intravascular coagulation and rhabdomyolysis. His aspartate aminotransferase peaked at 16,688 U/L, INR 9.3, creatinine kinase 253,377 U/L, creatinine 10.2 mg/dL, and troponin 29ng/mL. He required hemodialysis while in the medical intensive care unit (MICU) because of anuric renal failure, and he remained intubated for 9 days. His mental status returned to baseline by day 13 and his lab values except for his creatinine normalized by day 18. The patient required hemodialysis for 1 month, after which his creatinine normalized and his urine output returned to normal.

Using high performance liquid chromatography, urine from the day of admission was examined and found to have a 3,4 methylenedioxypyrovalerone (MDPV) level of 140 ng/mL. MDPV is a synthetic compound similar structurally to pyrovalerone, which is a potent inhibitor of the dopamine and norepinephrine transporters. Pyrovalerone is 9 times and 13 times more potent than cocaine at inhibiting the uptake of dopamine and norepinephrine, respectively. The exact mechanism responsible for the clinical course of this 25-year-old male is not certain, but it is presumed that MDPV was responsible for causing hyperthermia through a central dysregulation process. It is also possible that the elevated body temperature was due to an uncoupling effect of MDPV on skeletal muscle proteins and oxidative phosphorylation, or that is was due to increased muscle activity or agitation. Regardless, MDPV is strongly associated with causing hyperthermia. It is unknown, however, whether the end-organ effects seen in this patient were due to the direct cellular toxicity of MDPV or from the marked agitation and hyperthermia that subsequently ensued. Nonetheless, treatment of MDPV intoxication should be similar to the management of other sympathomimetic agents, which is aggressive supportive care and controlling of the patient's agitation with benzodiazepines.

Death Following Recreational Use of Designer Drug "Bath Salts" Containing 3,4-Methylenedioxypyrovalerone (MDPV). Murray BL, Murphy CM, Beuhler MC. *Journal of Medical Toxicology*. 8(1): 69-75.

This toxicology case report presents a 40-year-old male with a history of bipolar disorder who injected and snorted an unknown amount of bath salts containing MDPV. He subsequently became extremely agitated and went into cardiac arrest. It is the first reported case of confirmed isolated recreational MDPV use causing an excited delirium syndrome that ultimately progressed to death.

Shortly after abusing bath salts, a 40-year-old male became delusional and uncontrollably aggressive requiring police restraint. He was taken to the ED and continued to exhibit very aggressive behavior and incomprehensible screaming. The vital signs at triage were blood pressure 100/64 mmHg, heart rate 91 bpm, respiratory rate 12 breaths per minute, and oral temperature of 98.0°F (36.7°C). Within 5 minutes of arrival to the ED, the patient developed bradycardia that subsequently progressed to a pulseless electrical activity (PEA) arrest. Cardiopulmonary resuscitation (CPR) was initiated along with the administration of epinephrine, lidocaine, atropine, naloxone, and flumazenil. After 30 minutes of advanced cardiac life support (ACLS), return of spontaneous circulation was achieved.

Immediately after resuscitation, the patient was noted to be febrile with a rectal temperature of 105.4°F (40.8°C). His post-arrest laboratory evaluation was significant for a potassium of 7.4 mEq/L, creatinine of 3 mg/dL, and creatinine kinase of 234 U/L. His urine drug screen was positive for opiates. Repeat ECG showed peaked T waves and a prolonged QRS of 240 milliseconds. The patient was transferred to a tertiary care center with hemodialysis capabilities.

On arrival to the tertiary care center, the patient's temperature had decreased to 100.2°F (37.9°C) and the blood pressure remained low at 85/41 mmHg despite high doses of dopamine, phenylephrine and intravenous (IV) fluids. His neurological exam was significant for dilated and minimally reactive pupils, normal corneal reflexes, and an intact gag reflex. His ECG was significant for a right bundle branch block with a rate of 53 bpm and hyperacute T waves. A venous blood gas showed a pH 7.2 with a base excess of -11 mEq/L and a lactate of 2.83 mmol/L. Despite medical treatment with calcium gluconate, sodium bicarbonate and insulin, his potassium remained elevated at 8mmol/L.

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The patient was admitted to the MICU and treated with a sodium bicarbonate drip, vasopressin, hydrocortisone and normal saline. Despite these interventions, his metabolic acidosis gradually worsened over the following 3 hours to pH of 7.14 and he became anuric. His INR increased to greater than 9.3 and his creatinine kinase was 75,952 U/L. He developed an anemia (hemoglobin of 6.3 g/dL) and thrombocytopenia with platelets of 11×109/L. Hemodialysis was started 17 hours after initial presentation and he was transfused 4 units of packed red blood cells, 2 units of platelets, 9 units of cryoprecipitate and 10 units of fresh frozen plasma. Despite improvements in his acidosis and anemia, he deteriorated neurologically and at 42 hours after initial presentation he was declared brain dead by clinical criteria. Supportive care was withdrawn.

Throughout the patient's hospital course, several toxicology screens were performed and all were negative for barbiturates, amphetamines, benzodiazepines, cocaine, marijuana, methadone, opiates, salicylates, lithium, ethanol, ethylene glycol, methanol, and isopropanol. Samples of the patient's urine and serum were later screened using gas chromatography/mass spectrometry and found to be positive for acetaminophen, caffeine, cotinine, lidocaine, trimethoprim (12 mcg/mL), and MDPV (670 ng/mL).

Since 2010, MDPV has been the most commonly detected beta-keto phenylalkylamine found in toxicological analyses of bath salts in the U.S. This case report of MDPV toxicity initially described symptoms consistent with Excited Delirium Syndrome (ExDS). ExDS Is a specific type of delirium with agitation, hyperthermia, tachypnea, tachycardia, a period of decreased struggle, and then progressing to cardiac arrest. ExDS is most likely due to a dysregulation of dopaminergic pathways, which can be exacerbated by a recent history of cocaine use. This patient had a chronic history of cocaine abuse and he rapidly progressed from a state of agitated delirium to sudden PEA arrest. A return of spontaneous circulation was achieved, but subsequently there was the development of coagulopathy, rhabdomyolysis, renal and hepatic failure, anoxic brain injury and finally death. This case encourages emergency physicians and toxicologists to consider novel drugs of abuse in the differential diagnosis and test for it when indicated. This would help further characterize the symptoms related to intoxication and improve the understanding of the potential toxicities these newer drugs of abuse may have.

Centers for Disease Control and Prevention MMWR. *Weekly*/ Vol. 60/No 19. May 20, 2011.

This report summarizes the investigation of 35 people who had ingested, inhaled, or injected bath salts and subsequently visited a Michigan Emergency Department (ED) between November 13, 2010, and March 31, 2011. Michigan state public health agencies, health care providers, poison control centers, and law enforcement agencies coordinated their efforts to rapidly identify this emerging health problem and ultimately enabled an emergency public health order to remove the toxic bath salts from the marketplace.

From November 2010 to January 2011, the Marquette County ED treated 7 patients presenting with hypertension, tachycardia, tremors, motor automatisms, mydriasis, delusions, and paranoia. These patients had reported using bath salts purchased at a local store for about $20 per package. The number had increased to 13 by February 3, and on February 4th an emergency public health order was placed by the Marquette County Health Department and the owner of the local store was ordered to turn over all products known to contain MDPV to government authorities.

On February 5th, the Michigan Department of Community Health (MDCH) instituted a mandate requiring hospitals to report all cases of possible bath salts intoxication. The MDCH also started an investigation into bath salt abuse, and ultimately identified 35 patients who visited a Michigan ED during the period between November 13, 2010, and March 31, 2011. The patients ranged from 20-55 years of age: 19 (54%) were men and 16 (46%) were women. Twenty-four (69%) of the patients identified had a self-reported history of drug abuse, with 11 (31%) reporting polysubstance abuse and 12 (34%) intravenous drug abuse. Sixteen patients (46%) had a history of mental illness reported in their medical records including bipolar disorder, schizophrenia and depression. The method of abuse varied as 22 (63%) of the patients injected the drug, 9 (26%) snorted it, and 4 (11%) had ingested it. No relationship was identified between the exposure route and the severity of illness.

The clinical findings in the investigation were consistent with stimulant intoxication. Of the 35 identified patients, 32 (91%) had neurologic symptoms, 27 (77%) had cardiovascular symptoms, and 17 (49%) had psychological symptoms. Agitation (66%) and tachycardia (63%) were the two most common symptoms found in these patients. Delusions/hallucinations were also a frequent symptom seen in 40% of patients. Seventeen of the 35 patients were hospitalized, 15 were treated then discharged from the ED, 2 left against medical advice, and 1 was dead on arrival to the ED. Of the 17 hospitalized patients, 9 were admitted to the ICU, 5 to the general floor, and 3 were admitted directly to a psychiatric unit. Treatment consisted of supportive care, and benzodiazepines were used to control agitation.

Although bath salt abuse has been documented nationwide, this report is the first to summarize the epidemiology of a number of ED cases. The investigation demonstrated collaboration between public health, law enforcement and health care. The Marquette County Health Department issued an emergency order to decrease local bath salt abuse locally. In addition, a statewide system was established to mandate reporting of detected cases in other counties. These methods demonstrate the importance of identifying a potentially dangerous substance in a timely manner and implementing appropriate strategies to reduce further drug-related morbidity and mortality.

Conclusion:

Bath salts and synthetic cannabinoids are emerging drugs of abuse of which all emergency providers must be aware. Though treatment consists primarily of supportive care and the use of benzodiazepines to control agitation and anxiety, awareness of these drugs and patients' expected courses of intoxication can help predict complications and allow for the timely initiation of care. An increased awareness of their use in your community can help encourage public health awareness and interventions to remove these products from local stores.