Intranasal Substituted Cathinone "Bath Salts" Psychosis Potentially Exacerbated by Diphenhydramine

Erik W. Gunderson, MD, FASAM, Matthew G. Kirkpatrick, PhD, Laura M. Willing, BS, and Christopher P. Holstege, MD

Abstract: In this report, we describe a case of intranasal "bath salts"-associated psychosis. Symptoms developed during a 3-week binge and were potentially exacerbated by oral diphenhydramine taken for insomnia. The clinical case conference includes expert discussion from 3 disciplines: emergency medicine toxicology, behavioral pharmacology, and addiction medicine. It is hoped that the discussion will provide insight into the clinical aspects and challenges of addressing acute substituted cathinone toxicity, including acute psychosis, a major adverse effect of bath salts consumption.

Key Words: bath salts, designer drug, diphenhydramine, mephedrone, 3,4-methylenedioxypyrovalerone, psychosis

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CASE DESCRIPTION

The patient is a man in his late-20s, with chronic low back pain and long-term sustained remission of cocaine, alcohol, and opioid dependence on buprenorphine/naloxone maintenance (8/2 mg daily). His last cocaine use was 3 years ago. Currently, he has tobacco and cannabis dependence. Although he had stopped smoking marijuana several months before presenting with bath salts use, he continued to intermittently smoke synthetic cannabinoid products (eg, Spice, K2) on the weekends (for review, Gunderson et al., 2012). Psychiatrically, he has a history of major depressive disorder exacerbated by substance use, including cannabinoids, and was being treated with duloxetine for depressed mood and also chronic low back pain. He received monthly buprenorphine medication management counseling, along with counseling about motivation and relapse prevention that recently had focused primarily on marijuana and synthetic cannabinoid product use. With this regimen, his function was relatively stable regarding employment, family relations, and chronic pain, although he continued to have mild depressive symptoms and use synthetic cannabinoid products.

From the University of Virginia School of Medicine (EWG and CPH), Charlottesville; Center for Wellness and Change (EWG), Charlottesville, VA; Columbia University College of Physicians and Surgeons (EWG), New York, NY; University of Chicago (MGK), Chicago, IL; and University of North Carolina School of Medicine (LMW), Chapel Hill.

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Dr Gunderson provides consultation for MedicaSafe, Inc. (131 Varick St, Suite 934, New York, NY) and Orexo AB (Box 303 SE-751 05 Uppsala, Sweden). Neither company is involved in substituted cathinone or stimulant product development.

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Send correspondence and reprint requests to Erik W. Gunderson, MD, FASAM, University of Virginia Health System, University of Virginia School of Medicine, Box 800623, Charlottesville, VA 22908. E-mail: erikgunderson@virginia.edu.

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Phone Presentation

During a weekend night in 2011, one of the coauthors (EWG) received a mobile phone text message from a patient who stated that he had better photographs but not on his cell phone. An attached photograph showed a view looking out from a porch at night. As the patient did not identify himself in the text, the message was ignored as a possible wrong number. The following morning, another text referred to the coauthor as "Doc," and stated, "There here in a motel im at." The physician subsequently called the patient and had an hour-long phone conversation about recent events.

The patient stated that 3 weeks ago he began using bath salts, which was available over the counter, on the same shelf adjacent to several synthetic cannabinoid products. According to the sales clerk, the product included an amphetamine-like substance, which the patient thought he would try for its novelty. According to the patient, the phrase "not for human consumption" is code for a designer drug product with psychoactive effects, whether stimulant or synthetic cannabinoid in nature.

He purchased a 1/8 oz jar of bath salts, and with intranasal use, described the effect and smell as similar to that of cocaine but without nasal numbness. The onset of action was approximately 30 minutes. He continued daily bath salts use, reporting morning use, with cessation by 3 PM each day, for a 3-week period, using several products with brand names such as Infinity, TranQuility, Cool Wave, and White Lightning, the last of which was marketed as a stain remover. During the 3-week binge, he stopped buprenorphine/naloxone, duloxetine, and synthetic cannabinoid product use and did not use other illicit substances. He denied opioid-withdrawal symptoms, such as diaphoresis, abdominal cramps, nausea, vomiting, diarrhea, hot flashes, chills, or increased pain. However, he experienced progressive irritability and arguments with his family who said

he needed help. He noted substantial weight loss. His mind was racing and he had insomnia. He began hallucinating, seeing different "things," including people walking around his yard and house dressed in all white, having sex in his yard, and chanting. The photograph of the porch was an attempt to document 1 of these figures.

The hallucinations markedly increased at night, after taking diphenhydramine to "come down." Typically, he would take 8 to 10 Benedryl tablets (diphenhydramine, 25 mg). The night before sending the text message, the hallucinations had increased after taking diphenhydramine, which prompted him to climb onto his roof with a crossbow. He fired 2 arrows into the yard after giving the figures "the opportunity to identify themselves." He had transient suicidal ideation later in the night, which occurred after the number of people increased from what were "always" there, 3 individuals dressed in white to 6 to 7 individuals. His plan was to use the crossbow.

The following morning, when speaking to the coauthor by phone, the patient reported having spent the night at a hotel "trying to get off" bath salts, although he had just used it 15 minutes before the call. He was paranoid that people were breaking into his room but neither saw the figures nor had the crossbow with him. He had called the police the previous night, about the break-in. When they arrived to investigate, the patient did not disclose his bath salts use or psychotic symptoms. The police left after ascertaining that no break-in was taking place. During the conversation with the physician, the patient still believed a break-in was taking place. The physician discussed calling emergency medical services, but the patient declined to provide his location to avoid emergency medical services or further police involvement. After a long discussion, he agreed to have a friend drive him to a local emergency department (ED). After the phone conversation, the physician contacted the police department serving the region where the patient lived. They had a record of the visit to the hotel to investigate the break-in. The physician expressed concern about the patient's safety and risk to self and others. The police revisited the hotel approximately an hour later, but he had already gone with the friend to the ED.

ED Evaluation

Upon presentation to the ED, the patient was initially reluctant to disclose the psychotic symptoms but later reiterated the aforementioned history. He stated that agitation and fear about the break-in led to suicidal and defensive homicidal ideation. At one point, he was on the top of the building, threatening to jump off. He noted that the figures who were trying to break into his home disappeared when he shined a flashlight on them but then returned when he removed the flashlight. He tried to shoot them with the crossbow because they were threatening him.

On initial evaluation, his vital signs were as follows: blood pressure, 150/100 mm Hg; respiratory rate, 24 breaths per minute; and pulse rate, 114 beats per minute. He was noted to be anxious in the ED, but the rest of his physical examination was essentially unremarkable at the time of presentation. He did not see the figures in the ED setting, yet reported that the people who were trying to break in to his home and hotel were real. Thought content was notable for paranoia, suicidality, and defensive homicidality, including "threatening to kill his hallucinations." His laboratory values were significant for potassium (3.2 mmol/L), aspartate aminotransferase (65 IU/L); alanine aminotransferase 71 (IU/L); acetaminophen (not detectable), and ethanol (not detectable). A rapid bedside drug screen was positive for phencyclidine and benzodiazepines.

Because of concerns about his hallucinations and delusions, along with the risk to self and potential bystanders, the decision to admit the patient for bath salts abuse and bath salts–associated psychosis was made. The patient was monitored overnight. The following day, approximately 30 hours after the last-reported bath salts use, he was calm and his autonomic hyperactivity had resolved. On examination, it was found that his mental status, including thought content, had normalized, and he was discharged.

Clinical Course (3-Month Follow-up)

After discharge from the ED, he resumed buprenorphine/naloxone maintenance, without nonprescribed opioid use or cravings. He resumed duloxetine for another 2 weeks but stopped this without incident because of sexual side effects. Although he was able to abstain from bath salts use, he continued intermittent synthetic cannabinoid product use of less than 0.5 g per week, purchased over the counter and still available despite a federal ban. He denied use or cravings for cocaine. The psychotic symptoms had not recurred, and during the subsequent 3 months of monitoring, leading up to drafting this case report, he denied depression, anxiety, or thoughts about harm to himself or others.

The patient provided verbal consent for the case report submission and written consent to obtain the ED records. The case write up lacks Health Insurance Portability and Accountability Act identifiers and uses an ambiguous age range and slight modification in presentation to further protect patient identity, without impacting case analysis. The University of Virginia institutional review board deemed the case exempt from board review in August 2012.

DISCUSSION

Christopher P. Holstege, MD (Toxicology/Emergency Medicine)

Bath salts are Internet-acquirable synthetic drugs of abuse that typically contain a white powder that has been reported to be abused via multiple routes, including inhalation, ingestion, or injection. Bath salts can be purchased from a number of venues, including the Internet, head shops, convenience stores, or certain tobacco shops. Analytical testing of these products and testing of humans who have used these have found 3,4-methylenedioxypyrovalerone (MDPV), mephedrone, and methylone (Drug Enforcement Agency, 2011). 3,4-Methylenedioxypyrovalerone, mephedrone, and methylone are synthetic compounds that are structurally related to pyrovalerone and to cathinone, a stimulant found in the Khat plant, *Catha edulis*.

There is scantily available clinical information in the medical literature on bath salts misuse. Drug-induced psychosis and aggression seem to be more severe than that from

other amphetamine-like stimulants. The published reports of MDPV in clinical samples looked at testing samples in opioid-dependent patients or drivers suspected of being under the influence of drugs (Kriikku et al., 2011; Ojanpera et al., 2011). These initial reports focus on analytical methods and do not describe clinical data. Isolated published case reports do attribute various clinical effects (eg, psychosis, rhabdomyolysis, renal failure, hepatotoxicity, metabolic acidosis) to the use of bath salts, but lacked confirmatory analytical data (Penders and Gestrin, 2011; Ross et al., 2011; Striebel and Pierre, 2011). Spiller et al (2011) published a retrospective case series of bath salts–intoxicated patients who reported to 2 poison centers, some of whom had positive confirmatory testing results. However, these patients were also positive for numerous other substances of abuse and were not isolated bath salts abusers. Although the patient denied phencyclidine (PCP) consumption, the possibility exists for either PCP use or inadvertent exposure in bath salts products. However, factors pointing against a PCP effect include a lack of reported PCP detection in bath salts samples and a lack of dissociative symptoms. In addition, a false-positive urine toxicology screen due to diphenhydramine was commonly seen within the ED where the patient was treated.

Interpretation of such urine drug screens is commonly confounded by false-positive results (Brahm et al., 2010). The monoclonal antibodies used in these immunoassays may detect epitopes from multiple drug classes.

Despite the variety of potential substances that may be present within bath salts, it is important for clinicians managing these poisoned patients to follow basic poisoning care management. All patients presenting with toxicity should be managed supportively (Lawrence et al., 2007). If the patient is markedly agitated and at risk of harm to self or staff, he or she should be sedated. In an intoxicated, agitated patient, especially considering the sympathomimetic effects of those substances being reported with in bath salts, benzodiazepines are the preferred agent for initial sedation. If benzodiazepines are titrated to the calming of the patient, typically other abnormal clinical effects such as hypertension and tachycardia will also improve. The health care providers should place these intoxicated patients initially on continuous cardiac monitoring with pulse oximetry and perform frequent neurological reassessments to ensure clinical improvement and that adverse cardiac events do not develop. Adequate administration of intravenous fluids to ensure good urine output should be performed, as these intoxicated patients often are dehydrated. If symptomatic on presentation, laboratory testing should be broad and an electrocardiogram should be obtained, as nearly all organs are adversely impacted by the drugs found within bath salts (eg, rhabdomyolysis, acute renal failure, hepatotoxicity). If the patient has appropriately calmed, there is no evidence of significant end organ injury, and the patient's vital signs have normalized, then the patient can be discharged safely off cardiac monitoring.

Mathew Kirkpatrick, PhD (Behavioral Pharmacology)

This case study provides an interesting example of several fundamental concepts in behavioral pharmacology that we will describe in the following paragraphs, including (1) drugs of abuse are *reinforcers* of behavior; (2) after an extended period of abstinence, drug-taking behavior can be *reinstated* after a salient stimulus; and (3) *route of administration* influences acute drug effects. These concepts are essential to addiction medicine because they can potentially provide critical information about not only the role of the drug in maintaining problematic drug use but also the factors that may contribute to relapse.

As mentioned earlier and in the accompanying review, it is difficult to know the exact substance the patient ingested. Bath salts products are produced by several manufacturers, are neither standardized nor regulated, and packaging rarely includes a list of active ingredients. If the packaging lists ingredients or if the chemical is sold directly, the products often do not list the designer stimulant that they purport to contain. However, on the basis of the available forensic evidence from the Drug Enforcement Agency (DEA) (Drug Enforcement Agency, 2011), we can reasonably assume that the patient received methylone, mephedrone, MDPV, or some combination of these drugs, potentially along with other stimulants. Nevertheless, on the basis of his history and corroborative anecdotal reports of substituted cathinone users, it is likely from the patient's self-reported experience during his 3-week binge that he was taking a stimulant that had (1) a similar set of subjective effects to cocaine and (2) a similar behavioral profile—including sleep deprivation and psychosis after a series of large doses over an extended period of binge use—to a wide variety of stimulants, including the amphetamines (to which all 3 bath salts drugs are related).

Regardless of which drug the patient purchased and consumed, his case is an interesting example of *reinstatement* of drug-taking behavior. Reinstatement is a concept in behavioral pharmacology that refers to the resumption of drug-taking after a extended period of abstinence. Experimental animal research has helped to elucidate the reinstatement process. For example, in a typical animal laboratory experiment, subjects are trained to self-administer a drug (such as cocaine) by pressing a lever. After pressing a lever, the animal is given an injection of cocaine. This injection of cocaine is said to *reinforce* the behavior of lever-pressing, that is, receiving cocaine increases the likelihood that the animal will press the lever repeatedly to obtain more cocaine. This behavior (ie, lever-pressing or drug-taking) can be *extinguished* simply by ceasing the cocaine injections. The lever-pressing can be *reinstated*, however, with a single priming injection of cocaine or another stimulant (see Shaham et al., 2003 for a review). Reinstatement can also result from environmental cues, which, borrowing from the 12-step recovery community, is analogous to "people, places, and things" as potential factors leading to relapse.

It is possible that the patient in this case—a man who was in sustained full remission for cocaine dependence—experienced the initial dose of bath salts as a priming dose, and this led to reinstatement of his stimulant-taking behavior. This is interesting because although the compounds purportedly in bath salts are not structurally related to cocaine, they all increase synaptic levels of monoamine neurotransmitters, including dopamine, which has been implicated in reinstatement (Shaham et al., 2003) and drug-taking

behaviors in general (eg, Volkow et al., 2007). Furthermore, the patient reported that the bath salts produced subjective effects similar to that of cocaine. These effects could have acted as *interoceptive* (or internal) cues, triggering a relapse episode in much the same way that an environmental cue might. In other words, it is possible that the patient resumed his former problematic cocaine-taking behavior, although he was likely not exposed to cocaine. This would suggest that, for abstinent cocaine users, any stimulant use could result in relapse, with potential damaging consequences.

It is important to note that this is one individual case study and may not generalize to the larger recreational drug-using population. Systematic study is needed, from laboratory studies investigating the substituted cathinones under controlled, double-blind conditions with larger (an appropriately powered) sample of participants, for adequate comparison. Thus, it is difficult to determine from this case what the effects and toxicity risks of the compounds associated with bath salts might be. For example, several uncontrolled factors might have influenced this patient's experience, including expectancies, lack of experience with these compounds, psychiatric comorbidity, and concurrent substance and medication use, including diphenhydramine. One factor that is known to influence the effects of a drug is the *route of administration*. This patient nasally insufflated the bath salts. The intranasal route of administration is associated with a faster onset of effects than the oral route. Considering that the rapidity of drug effect onset is linked to the intensity of drug effects and the abuse potential of a drug (Hatsukami and Fischman, 1996), it is possible that the use via nasal route, similar to how he previously used cocaine, may have contributed to greater risk of negative consequences than a slower route of administration (such as oral). Of course, this is speculative; clearly, we need data from controlled laboratory settings to further characterize the effects of these drugs across a range of doses and through different routes of administration.

Finally, it is important to note that we have little information about how many individuals are using these drugs and the proportion of negative outcomes associated with them. As stated in the accompanying review, bath salts compound availability is relatively recent and data have not yet been reported from major national surveys. By and large, our information comes from poison control and the DEA, 2 organizations that, by definition, focus primarily on deleterious drug effects. Although it is not clear how many individuals use these drugs without experiencing severe negative effects, nonclinical sample survey data suggest that a substantial minority experience at least intermittent adverse effects, including potential dependence (Winstock et al., 2011a,b). Yet, it remains unclear what the relative abuse potential of these drugs are. Methylone, mephedrone, and MDPV are chemically related to the amphetamines, including methamphetamine and MDMA. Although it is widely believed that the relatively small chemical differences between methamphetamine and MDMA result in 2 drugs with widely varying abuse potentials (with methamphetamine being the drug with a greater abuse potential), under controlled laboratory conditions, MDMA, methamphetamine, and D-amphetamine produce many overlapping prototypic stimulant effects (Kirkpatrick et al., 2012a,b). Thus, the substituted cathinones in bath salts and other designer stimulant products could have varying abuse potentials (or differential in toxicity, in general), either to a greater or lesser extent than the more established amphetamines. Controlled human laboratory data are needed to understand the behavioral psychopharmacology of these compounds, which will help inform clinical practice, prevention, and health policy development.

Erik Gunderson, MD, FASAM (Addiction Medicine)

The case presentation provides insight into several biopsychosocial and clinical aspects of the growing bath salts trend, which poses a concerning challenge for addiction treatment providers, other clinicians, and society at large. Bath salts and other designer stimulants falsely labeled as household products potentially include several substituted cathinone compounds, including mephedrone, methylone, and MDPV (Drug Enforcement Agency, 2011). The cathinones facilitate monoamine release and reuptake inhibition similarly to cocaine and amphetamines. The compounds, in general, seem to exert sympathomimetic effects that may be complicated by psychopathological, cardiovascular, and neurological toxicity.

The patient's new onset of substituted cathinone product use reflects the recent availability of these designer stimulant products in the United States, which seems to persist despite state and federal prohibition and widely publicized, substantial consequences. The patient reflects the demographics of typical designer stimulant product users, who frequently have been young males (Drug Enforcement Agency, 2011). Co-occurring substance use among these individuals is widespread. The current case was no exception; he currently smoked synthetic cannabinoid products and during the period of substituted cathinone product use, took nonprescribed benzodiazepines and diphenhydramine to counter the stimulant effects.

The acute adverse consequences experienced by the patient add to a growing anecdotal literature about toxicity of substituted cathinone product consumption that includes risk of psychosis. During the 3-week binge, he progressed from irritability to psychosis associated with auditory and visual hallucinations, paranoia, and suicidal ideation. The psychotic symptoms resolved with supportive treatment approximately 24 hours after the last intranasal use, and the patient returned to his psychiatric baseline. Similar reports from bath salts use are suggested from calls to poison control centers and ED visits (Centers for Disease Control and Prevention, 2011; Spiller et al., 2011), although psychotic symptoms may persist longer in some patients. The report has several limitations, however, including a lack of substituted cathinone chemical confirmation, concurrent substance use, and other potential contributing factors.

Notably, the patient experienced an exacerbation in psychosis after taking diphenhydramine to "come down" at the end of the day, which is a potential interaction with bath salts stimulants that has not yet been reported. Diphenhydramine is a commonly available over-the-counter antihistamine often used for its sedative and somnolent qualities. Anticholinergic toxicity of diphenhydramine that includes psychosis might be expected to occur at much higher doses

than reported by the patient, and no anticholinergic signs or symptoms were noted in the ED record. Yet the possibility of an interaction between diphenhydramine and bath salts seems plausible, particularly in light of the temporal relation with increased symptoms after diphenhydramine dosing that occurred repeatedly over several days. With its perceived safety profile, some treating physicians may be inclined to recommend diphenhydramine among substance-using patients to avoid abusable and dependence-inducing medications such as benzodiazepines, and the medication has been prescribed for acute bath salts toxicity (Spiller et al., 2011). Furthermore, designer stimulant users like our patient may elect to use diphenhydramine products, as they are inexpensive and readily available. However, antihistamine use for sedation and insomnia due to bath salts use may not be advisable because of a potential adverse interaction, which requires further study.

Other factors potentially contributing to the patient's psychiatric symptoms include abrupt cessation of buprenorphine, duoloxetine, and synthetic cannabinoid products. Although it is plausible that the cessation of synthetic cannabinoid product use could worsen mood, given the potential crosstolerance with delta-9 tetrahydrocannabinol (Gunderson et al., 2012), psychosis due to delta-9 tetrahydrocannabinol, opioid, or duloxetine abstinence would be atypical, and the patient has not experienced such effects from abrupt cessation on other occasions.

The patient had a history of cocaine dependence, which may have increased his risk for rapid escalation and uncontrolled bath salts use, given an overlapping pharmacological mechanism and potential environmental and drug-related cues discussed in the Mathew Kirkpatrick, PhD (Behavioral Pharmacology) section. The patient described the subjective effects of intranasal bath salts use as similar to that of cocaine. Among music club attendees in the United Kingdom, with prior mephedrone and cocaine use, a majority rated mephedrone consumption as providing a longer lasting and better high than cocaine (Winstock et al., 2011a). In particular, intranasal mephedrone users rated mephedrone as being more addictive than cocaine (Winstock et al., 2011a), and intranasal bath salts administration may have increased the risk for binge use in the current case. Although the patient did not experience nasal numbness from the designer stimulant products, some substituted cathinone product manufacturers add benzocaine and lidocaine presumably to mitigate nasal irritation (Brandt et al., 2010). By mimicking the cocaine-taking experience, the presence of anesthetics in some designer stimulant products could serve as an overlapping interoceptive or internal cue for continued stimulant product use.

In addition to behavioral pharmacological factors contributing to the bath salts binge, we also must examine the patient's overall state of recovery as a potential risk factor for initiation and escalation and a target for improvement during aftercare. Although his cocaine dependence seemed quiescent, without recent cravings or thoughts about returning to use, he had multiple substance dependencies, was actively using synthetic cannabinoids, and accessing minimal substance treatment services. Similar to many substituted cathinone users, his decision to try bath salts was based on novelty-seeking and desire to try a legal stimulant substitute. Unfortunately, designer drug use screening among patients receiving substance use treatment is complicated by a lack of readily available diagnostic urine testing. As such, routine inquiry about designer stimulant use seems prudent, particularly among patients with a history of stimulant use disorders or among those using other designer drugs, which in the current case included synthetic cannabinoid products. Although the acute psychotic episode passed and the patient seemed to get back to "baseline," it remains concerning that he is not engaged in more structured substance treatment. Little information is available to guide the treatment for substituted cathinone dependence. However, national guidelines on stimulant-use disorder treatment (Substance Abuse and Mental Health Services Administration, 2009) provide a starting point that should be made available for the current patient to hopefully improve his overall recovery and outcome.

Last, the initial point of contact with the patient via text messaging warrants mention. Communication with patients via text is a reality of clinical correspondence that has come about in the past decade. Many patients are comfortable communicating via text messaging, including the current patient in the setting of acute psychosis. However, text-messaging limitations could lead to miscommunication, such as with the current case in which physician misinterpretation of the initial message led to a delayed response and could have led to an untoward outcome.

SUMMARY

Bath salts and other falsely labeled household products are a concerning stimulant drug use trend. The designer products include substituted cathinone chemicals and are associated with toxicity such as agitation and acute psychosis, as exhibited in the current case. During a 3-week binge, the patient developed psychosis that was potentially exacerbated by diphenhydramine and resolved with supportive care. Although the case report highlights a concerning adverse effect of bath salts consumption, a greater understanding of the behavioral pharmacology, health effects, and management of substituted cathinone use remains urgently needed.

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