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Selected Topics: Toxicology

SYNTHETIC CATHINONES ("BATH SALTS")

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☐ **Abstract—Background: Synthetic cathinones are popularly referred to in the media as "bath salts." Through the direct and indirect activation of the sympathetic nervous system, smoking, snorting, or injecting synthetic cathinones can result in tachycardia, hypertension, hyperthermia, myocardial infarction, and death. Objective: The chemical structures and names of bath salts identified by the Ohio Attorney General's Bureau of Criminal Investigation are presented. Based on their common pharmacophores, we review the history, pharmacology, toxicology, detection methods, and clinical implications of synthetic cathinones. Through the integration of this information, the pharmacological basis for the management of patients using synthetic cathinones is presented. Discussion: Synthetic cathinones activate central serotonergic and dopaminergic systems contributing to acute psychosis and the peripheral activation of the sympathetic nervous system. The overstimulation of the sympathetic nervous system contributes to the many toxicities reported with bath salt use. The pharmacological basis for managing these patients is targeted at attenuating the activation of these systems. Conclusions: Treatment of patients presenting after using bath salts should be focused on reducing agitation and psychosis and supporting renal perfusion. The majority of successfully treated synthetic cathinones cases have used benzodiazepines and antipsychotics along with general supportive care.**

☐ **Keywords—sympathomimetic; synthetic cathinones; amphetamine; phenethylamine; bath salts**

INTRODUCTION

Phenylisopropylamine and α-methylphenethylamine are chemical names for the clinically used but also commonly abused medication amphetamine. Amphetamine was initially synthesized in 1887 by the German chemist Edeleano as part of a series of compounds to improve upon ephedrine (1). Amphetamine is a synthetic compound that is not based on a natural product like ephedrine. Physicians noted the potential for amphetamine abuse and addiction, even in the context of medical use, as early as the 1940s (2). Amphetamine and its N-methyl analogue methamphetamine were used extensively by both Japanese and German armies to stimulate soldier efforts during World War II (3). After the war, Japan made amphetamines readily available without a prescription. Subsequently, the rates of amphetamine abuse and addiction escalated (4). In the United States, the initial epidemic of amphetamine abuse emerged in the 1960s, and regulatory efforts that included classifying amphetamine as a Schedule II controlled substance under the Controlled Substance Act and increasing regulatory control over the manufacturing and distribution of amphetamine were marginally effective (5). However, as regulatory and law enforcement officials focused efforts to reduce amphetamine abuse, an amphetamine analogue 3,4-methylenedioxymethamphetamine (MDMA) began to emerge in the illicit drug scene (6).

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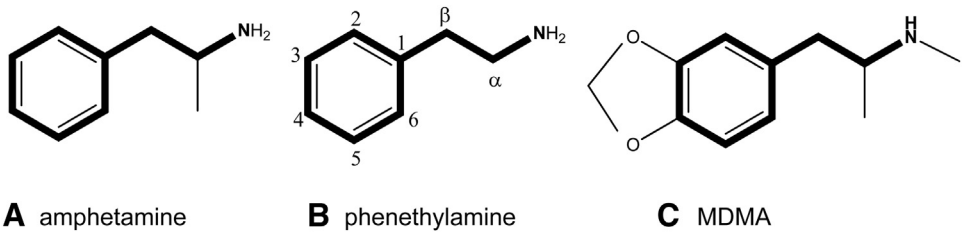


Figure 1. General chemistry of phenethylamine, amphetamine and 3,4-methylenedioxy-methamphetamine (MDMA). The phenethylamine pharmacophore is bolded in each of the structures. The α and β-carbons are the sites of many substitutions to the "bath salts."

MDMA was first synthesized in 1912 by Merck Pharmaceutical, but the compound remained largely ignored by both the scientific community and illicit drug users until the late 1970s, probably because of the availability of amphetamine and methamphetamine (7). In one of the first scientific reports, Shulgin et al. noted that MDMA induced an "easily controlled altered state of consciousness with emotional and sensual overtones" (8). These pharmacological effects of MDMA were in stark contrast to the hyperarousal, compulsive and sometimes paranoid behaviors from amphetamine use (9). Reasons for these differential pharmacological effects between MDMA and methamphetamine are ostensibly linked to the chemical structure differences (discussed in the next section). MDMA was placed on the Drug Enforcement Agency's Schedule I list of controlled substances in 1985 (10).

Presently, the latest versions of sympathomimetic compounds to emerge as abused drugs are the synthetic cathinone derivatives. Cathinone is a naturally occurring β-ketone analogue of amphetamine found in the leaves of the *Catha edulis* plant indigenous to northeast Africa and the Arabian Peninsula. Methcathinone, the N-methyl analogue of cathinone, was first synthesized in 1928 (11). These compounds are commonly classified in the popular media as "bath salts" because of the packaging and distribution techniques used by the illicit manufacturers to circumvent the Federal Analog Act. These synthetic cathinone compounds are not chemically or pharmacologically similar to epsom bath salts, but are central nervous system active drugs that are chemically and pharmacologically similar to amphetamine and MDMA.

CHEMISTRY AND HOW IT PREDICTS PHARMACOLOGY

The chemical structure of amphetamine and MDMA are shown in Figure 1 and are presented in order to identify the region of the substance known as the pharmacophore. The pharmacophore of a chemical structure is the portion of the structure that confers the substance's activity. In the case of amphetamine and MDMA, these drugs have the exact same pharmacophore (phenethylamine; see Figure 1). Because of this, MDMA would be considered a chemical analogue of amphetamine. Comparing the three structures further, the phenethylamine pharmacophore can be identified in all agents. Amphetamine has the addition of a methyl group off the α-carbon; hence the chemical name for amphetamine is α-methylphenethylamine. MDMA has the addition of the methyl group off the terminal amine generating the methamphetamine portion of the molecule. Increasing carbon substitutions has the ability to increase lipophilicity and, in some cases, protect against enzyme degradation. MDMA further has the methylenedioxy substitution off the three and four carbons. All these substitutions are responsible for MDMA's chemical name, 3,4-methylenedioxy-methamphetamine. Therefore, amphetamine and MDMA would have a predictably similar pharmacological activity (12,13).

The synthetic cathinones are chemical analogues of methcathinone and are classified chemically as β-ketone due to the carbonyl group (=O) at the β-carbon (see Figure 2). The synthetic cathinones also differ between each other in the length of carbon substitutions off the α-carbon and nitrogen (N) terminus. Through the addition of electron withdrawing groups such as fluorine (F) or increasing carbon length, the lipophilic nature of the synthetic analogue can be increased. The addition of carbons to the N-terminus is referred to as N-alkylation. N-alkylation maintains the stimulant activity of phenethylamine analogues (14–16).

Based on the structure–activity relationships of these phenethylamine analogues, synthetic cathinones and MDMA analogues would be predicted to have very similar pharmacological effects. Table 1 presents the chemical structures and names of novel bath salts identified by the Ohio Attorney General's Bureau of Criminal Investigation. Not all the agents listed in Table 1 have been pharmacologically tested in controlled human or animal studies. Most of the agents presented have also not been scheduled by the Drug Enforcement Administration. However, these synthetic cathinones, in general, have been shown to increase monoamine concentrations in the synaptic

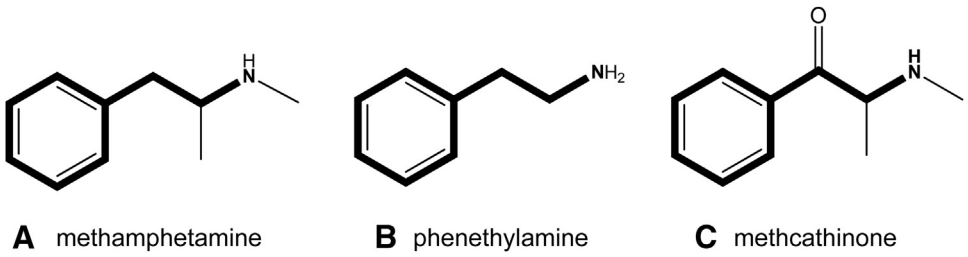


Figure 2. Comparison of the substituted cathinones (methcathinone) to substituted amphetamines (methamphetamine) and the phenethylamine pharmacophore. The phenethylamine pharmacophore is bolded in each of the structures. Methamphetamine has a methyl (single carbon) off the α-carbon and nitrogen (N) terminus of phenethylamine. Methcathinone has carbonyl group (=O) off the β-carbon of methamphetamine.

cleft (12,17–19). The increase in synaptic monoamines results in the stimulant and hallucinogenic effects of these phenethylamine analogues (12,17,19). The endogenously produced catecholamine monoamines (dopamine, norepinephrine, and epinephrine) are also phenethylamines.

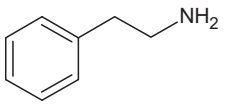
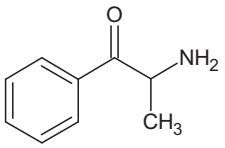
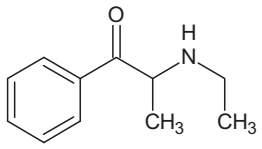
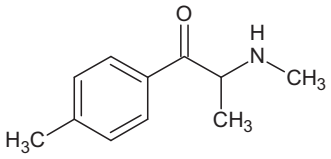
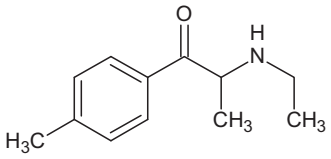
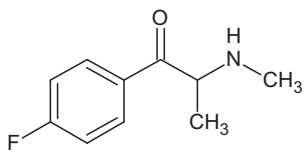
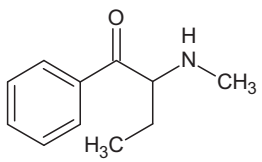
PHARMACOLOGY OF PHENETHYLAMINES

The shared phenethylamine pharmacophore between the endogenous monoamine neurotransmitters (dopamine and norepinephrine) and analogues of amphetamine and synthetic cathinones allows us to make predictions about the pharmacology of these abused compounds. For example, we would predict that these compounds would serve as substrates for the presynaptic monoamine transporters (dopamine transporter [DAT], norepinephrine transporter [NET], and serotonin transporter [SERT]), which are responsible for the reuptake of released monoamines from the synaptic cleft into the presynaptic neuron to terminate the effects of that monoamine on the post-synaptic receptor and to recycle the monoamine for re-release (see Figure 3).

Biochemical studies examining the effects of amphetamine and methamphetamine on these monoamine transporters confirm this prediction (19). Amphetamine is about threefold selective for the NET vs. DAT and about 70-fold selective for DAT vs. SERT. In contrast, methamphetamine is about 2-fold selective for the NET vs. DAT and about 30-fold selective for the DAT vs. SERT. The addition of the N-methyl group to amphetamine to produce methamphetamine resulted in a slight decrease in NET vs. DAT selective and a significant decrease in DAT vs. SERT selectivity. Next, adding a methylenedioxy bridge to the phenyl ring of methamphetamine changes the compound to MDMA. The addition of this group increases the selectivity for NET vs. DAT (approximately fivefold), but now MDMA is sevenfold more selective for SERT vs. DAT. Therefore, the addition of the methylenedioxy bridge "flipped" the DAT vs. SERT selectivity in favor of more SERT selective. Finally, if we add the β-ketone group to the methamphetamine pharmacophore to make methcathinone, we lose selectivity for NET vs. DAT, such that the ratio is now 1:1, but significantly increase the selectivity for DAT vs. SERT (120-fold) compared with methamphetamine (20). Cyclization of the aliphatic chain off the terminal amine (as in 3,4-methylenedioxy-α-pyrrolidinopropiophenone; Table 1) has been demonstrated to decrease the neurotransmitter release activity. This cyclization of the aliphatic chain, however, maintains the reuptake inhibiting effects (21). Overall, these biochemical studies highlight that relatively simple changes in the chemical structure can have profound effects on the selectivity of these compounds to act as substrates for and induce release of the different monoamine neurotransmitters and ultimately alter the abuse potential of these compounds.

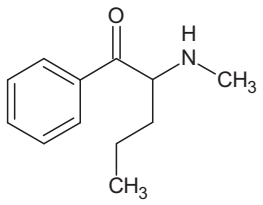
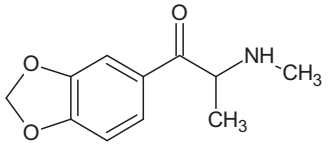
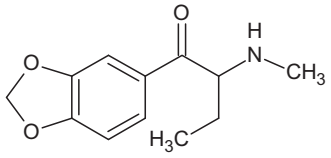
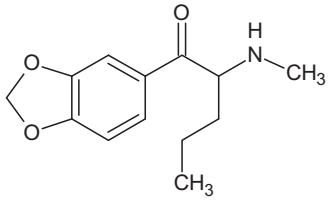
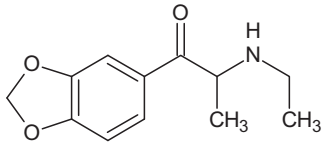
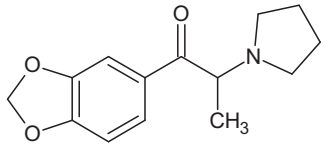
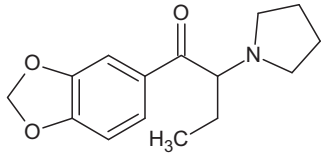
Increases in the neurotransmitter dopamine appear to be primarily responsible for producing the euphoric "abuse" effects of these compounds (22,23). Although Rothman and colleagues have argued that the potency to release norepinephrine compared with dopamine is a better predictor of the subjective effects of amphetamine and amphetamine analogues in humans (19). As discussed earlier, norepinephrine also has a significant role in the activation of both central and peripheral mechanisms of the sympathetic nervous system. Increases in the neurotransmitter serotonin produced by these compounds appear to have two main effects. First, significant increases in serotonin may produce the serotonin "syndrome" clinically manifested as tachycardia, hypertension, diaphoresis, and hyperthermia (24). Secondly, the selectivity of these compounds to increase dopamine vs. serotonin levels appears to have an impact on the abuse of these compounds, such that dopamine-selective compounds, like amphetamine and 3,4-methylenedioxypyrovalerone, have a higher abuse liability than serotonin-selective compounds, like fenfluramine and 4-methylmethcathinone (mephedrone) (25). How these compounds differentially alter levels of dopamine, norepinephrine, and serotonin in the brain and how this impacts both the abuse potential and the physiological consequences of these compounds that

Table 1. Bath Salts Identified by the Ohio Attorney General's Bureau of Criminal Investigation Using Gas Chromatograph and Mass Spectrometer

Structure	Name
	Phenethylamine Pharmacophore
	Cathinone DEA Schedule I
	Ethcathinone Not scheduled by the DEA
	Mephedrone DEA Schedule I
	4-methylethcathinone (4-MEC) Not scheduled by the DEA
	4-fluoromethcathinone DEA Schedule I
	Buphedrone Not scheduled by the DEA

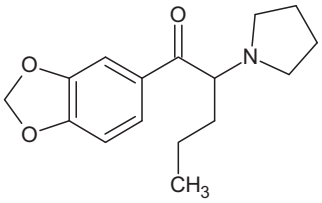
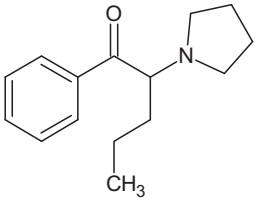
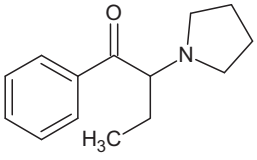
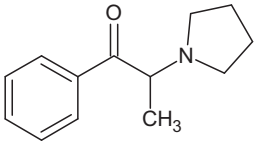
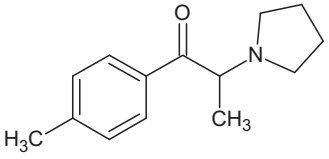
(*Continued*)

Table 1. Continued

Structure	Name
	Pentedrone Not scheduled by the DEA
	Methylone DEA Schedule I
	Butylone Not scheduled by the DEA
	Pentylone Not scheduled by the DEA
	Ethylone Not scheduled by the DEA
	3,4-Methylenedioxy-α-pyrrolidinopropiophenone (MDPPP) Not scheduled by the DEA
	3,4-Methylenedioxy-α-pyrrolidinobutiophenone (MDPBP) Not scheduled by the DEA

(*Continued*)

Table 1. Continued

Structure	Name
	3,4-Methylenedioxypyrovalerone (MDPV) DEA Schedule I
	α-Pyrrolidinovalerophenone (Alpha-PVP) Not scheduled by the DEA
	α-Pyrrolidinobutiophenone (Alpha-PBP) Not scheduled by the DEA
	α-Pyrrolidinopropiophenone (Alpha-PPP) Not scheduled by the DEA
	1-(4-methylphenyl)-2-(pyrrolidinyl)-1-propanone (MPPP) Not scheduled by the DEA

DEA = US Drug Enforcement Administration.

lead to emergency department visits are active areas of research.

DISCUSSION

Implications for the Clinician

As their pharmacophores would predict, smoking, snorting, or injecting synthetic cathinones can cause clinical symptoms and medical complications that combine the worst features of methamphetamine and MDMA.

Like methamphetamine and MDMA, bath salts enhance sympathetic nervous system activity. This can result in tachycardia, hypertension, and occasionally self-reported discoloration of the hands (presumably from peripheral vasoconstriction) (26). The severity of cardiovascular effects is highly variable, with some case reports describing only mild tachycardia (eg, heart rate [HR] < 120 beats/min) and others more serious (eg, HR > 150 beats/min, myocardial infarctions) (27,28). These differential effects are likely related to which synthetic cathinones are used, the amounts taken, and the time

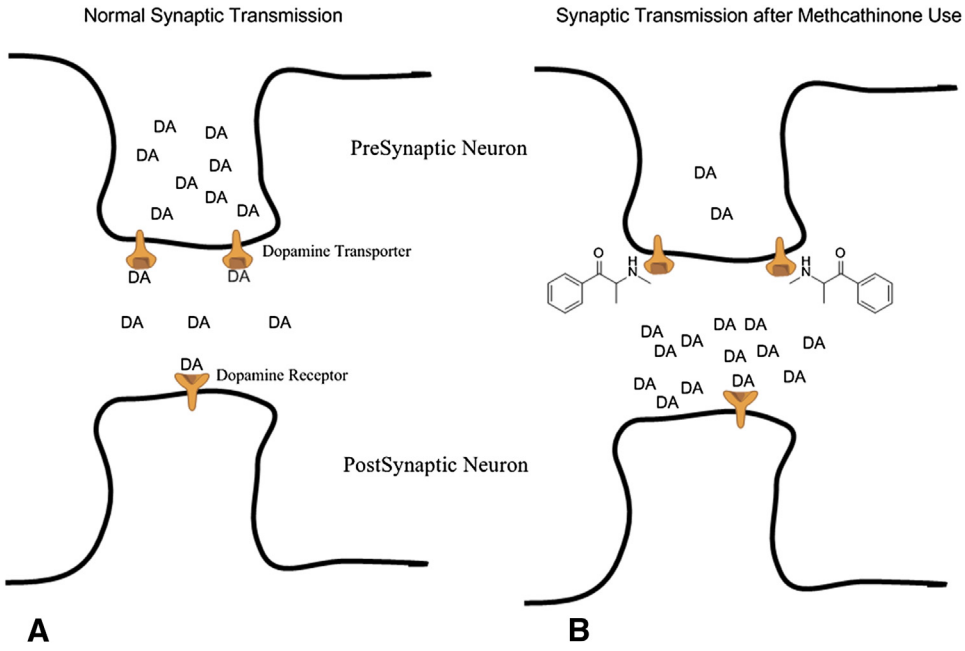


Figure 3. Simplified schematic of synaptic neurotransmission for the endogenous monoamine dopamine (DA). (A) Shows that under normal (nondrug) conditions, DA is released from the presynaptic neuron into the synaptic cleft, where DA can bind to post-synaptic DA receptors on the postsynaptic neuron to promulgate neurotransmission. DA can also bind to the DA transporter located on the presynaptic neuron and be translocated back into the presynaptic neuron for repackaging and subsequent release. DA uptake by the DA transporter is the primary mechanism of terminating the DA-mediated neurotransmission. (B) Shows that under conditions of methcathinone use, there is an increased concentration of DA in the synaptic cleft that results in increased activation of post-synaptic dopamine receptors. Also, methcathinone is a substrate for the DA transporter, blocking the ability of DA to bind to the transporter, and reducing one of the main mechanisms of dopaminergic neurotransmission termination.

from drug use to presentation at a hospital. What is evident in these case reports is that tachycardia is more severe and more prevalent than hypertension; heart rates are commonly reported > 150 beats/min, while concomitant blood pressure (BP) might be normal or only mildly (systolic BP < 150 mm Hg) elevated (29–31). This may reflect greater increases in circulating epinephrine and dopamine compared with norepinephrine. If true, this would make selective β-blockers a poor choice for controlling heart rate, as has been reported with cocaine, as they can cause unopposed α-stimulation with worsening hypertension and coronary artery vasoconstriction (32). While their mechanisms of action likely increase the risk of developing myocardial ischemia, to date ST-elevation myocardial infarction has not been reported. There have been cases of agitated delirium from bath salts in which elevated cardiac enzymes are reported (33).

Consistent with previous case reports involving methamphetamine and MDMA, large ingestions or repetitive use of bath salts can cause a severe agitated delirium, seizures, and life-threatening hyperthermia with concomitant cardiovascular collapse, renal failure, hepatic dysfunction, disseminated intravascular coagulation, and ultimately death (31,34,35). It is estimated that the mortality rate of patients using stimulants who present with body temperatures > 40.5°C is upwards of 50% (36). Sympathomimetic agents such as MDMA and methamphetamine increase body temperature by preventing heat dissipation via α_1-mediated peripheral vasoconstriction and by generating heat through the activation of mitochondrial uncoupling proteins (UCP3) (37,38). Adrenergic activation by these agents results in peripheral norepinephrine release and subsequent activation of α_1- and β_3-adrengergic receptors (AR) (39–41). β_3-AR activation leads to cyclic adenosine monophosphate−mediated stimulation of hormone sensitive lipase and subsequent release of free fatty acids (FFA). FFA can initiate facultative thermogenesis, a process by which adenosine triphosphate synthesis is "uncoupled" from substrate oxidation by FFA forming a proton-conductive pore in mitochondrial UCP3 located in skeletal muscle (38,42,43). Additionally, the elevations in plasma norepinephrine and epinephrine increase blood pressure and heart rate.

In addition to releasing norepinephrine, dopamine, and epinephrine, many of the bath salts, by virtue of their ring substitutions, cause increases in extracellular concentrations of serotonin. Therefore, in addition to traditional sympathomimetic findings, patients can also

develop serotonin syndrome with clonus and muscle rigidity (44). As it can be difficult to clinically differentiate between the sympathomimetic and serotonin syndrome, the clinical management of these patients should focus on the use of benzodiazepines. While cyproheptadine, an anti-serotonergic agent, has been used in managing symptoms from bath salts, it can only be given orally and should be considered an adjunct therapy (44,45).

Renal failure is a clinical manifestation of bath salt use that has also been reported with methamphetamine and MDMA. Renal failure after bath salts can be part of the multisystem organ failure seen in cases of severe sympathomimetic syndrome, or it can present as a complication of isolated rhabdomyolysis (31,33,45). Although bath salts are relatively new to the drug abuse scene, there have been numerous cases of rhabdomyolysis, and three reported cases of rhabdomyolysis from muscle compartment syndrome (28,30,46). The large percentage of cases reported with bath salts suggests they may have a great predilection for causing muscle damage. Clinicians should be aware of this potential in young adults presenting to the hospital with acute muscle pain. Renal failure can also be present without rhabdomyolysis or multisystem organ failure (28,47). Although the mechanism behind these "isolated" cases of renal failure is not known, many of the patients abusing bath salts go on multi-day binges, during which they exert themselves excessively but eat and drink little. As such, it is likely that many of these cases are prerenal acute tubular necrosis from dehydration; a supposition that is supported by the finding that, in many of these cases, renal insufficiency rapidly resolves with fluid resuscitation (48).

Although MDMA use has rarely been associated with isolated liver failure, there have not been similar cases reported to date with bath salts; although cases have been reported associated with multisystem organ failure from their use (31,35). Whether this is secondary to differences in the pharmacophore of MDMA and the synthetic cathinones, differences in contaminants, or is simply of a matter of time is not yet known.

The most common clinical effect associated with bath salt use is the development of acute psychosis. Although this has been well described with methamphetamine, and occasionally reported after MDMA, it appears to be particularly problematic for bath salt users. In published case series and in most of case reports, the most common presenting clinical sign of patients taking bath salts is psychosis (27,29,49–52). In many of these cases, patients suffer from paranoia, visual and auditory hallucinations, and can be self-injurious or homicidal (29,53). Many of these patients also report amnesia surrounding their psychotic breaks (54,55). As with methamphetamine, the cause is likely related to altered dopaminergic neurotransmission (50). Antipsychotics attenuate dopaminergic activity and have been successfully utilized in the management of synthetic cathinone–induced psychosis (29,51). Another contributing factor can be insomnia; in many of the cases, patients report being awake for days (54,55). It is important for the clinician to note that the psychosis induced by bath salts can present without the presence of acute sympathomimetic effects (53,56,57). Bath salts, therefore, should be considered in any young adult presenting with new-onset psychosis. Although the majority of patients with bath salt psychosis have had a history of prior drug abuse, most of them had not had prior episodes of psychosis (29). It is not clear if the increased incidence of psychosis with these cathinones is related to drug chemistry, potency, contaminants, or may be a consequence of more frequent use. This is of particular interest, as many of these drugs have been legally sold in corner convenient stores, making them much easier to obtain than illegal methamphetamine or MDMA.

Similar to MDMA, use of bath salts has been associated with the development of hyponatremia and cerebral edema (58,59). As with MDMA, bath salts likely cause hyponatremia by increasing the release of vasopressin, an effect that can be mediated by serotonin (60).

A rare complication reported that appears to be somewhat unique to bath salts is hypoglycemia. To date there have been three cases reported in which patients have had low blood sugar (35,61). The etiology of this is not known, but bath salts users often binge for several days during which they may eat very little. As both methamphetamine and MDMA, and presumably bath salts, release insulin in animals, this combined with decreased local stores of glucose could cause hypoglycemia (62,63). It is of interest, however, that hypoglycemia is not commonly reported with MDMA or methamphetamine, suggesting that there could be metabolic effects unique to bath salts.

DETECTION OF SYNTHETIC CATHINONES

Synthetic cathinones are not always detected in routine urine drug screens. Therefore, if confirmation testing is required, urine or blood samples need to be sent to forensic laboratories specializing in the detection of cathinones. As send-out testing can take a week or longer, the decision to test for bath salts should be based primarily on diagnostic, forensic, or public health needs. For instance, a young patient presenting with new-onset psychosis or agitated delirium should have samples collected for testing to help clinicians differentiate between drug-induced psychosis and mental illness. Similar testing should be done for new onset seizures, stroke, renal failure, or rhabdomyolysis in a young adult. Bath salts have a

variety of structures and as soon as one compound is made illegal to sell and possess, a new one arrives on the black market. This can result in clusters of clinical presentations and deaths. This makes it imperative for emergency department physicians to work with their local Poison Center, Toxicology Center, Health Department, and Law enforcement to help identify what is currently being sold and distributed in their area. This can help facilitate both educational and law enforcement efforts.

The most commonly used instrumentation for detection of controlled substances is a gas chromatograph (GC) coupled with a detection system to confirm structure, such as a mass spectrometer (MS) or an infrared detector (IRD). This combination is desirable because the GC separates compounds in a mixture based on size, while the MS or IRD can deduce the different functional groups that can identify an individual compound. Although no one system is perfect, using multiple systems on a single sample will often yield more conclusive results.

Separating a mixture using GC is essential to identifying each individual compound. An illicit drug is often "cut" or diluted with an additional, inexpensive substance in order to increase profit for the supplier or dealer. This cutting can complicate detection of the illicit substance. The separation facilitated by the GC simplifies this problem. Although coupling the GC with a MS or IRD is preferable, valuable information can also come from size separation alone. A secondary test is to run the evidence sample and a known standard consecutively and compare the migration time. Although not confirmatory, this method is often utilized as a secondary assay once the identity of a substance is known.

The MS is likely the most often used detector in drug chemistry. A mass spectrum is easily created using now common instruments with highly reproducible results and mass spectra of nearly all known licit and illicit chemicals can be found in the scientific community.

The IRD has an advantage over the MS in the respect that the IRD can distinguish positional and optical isomers. Although the MS can provide data suggesting an isomer, further testing would be required to prove the existence of that isomer. The method of structure analysis used by an IRD would immediately indicate the identity of an isomer, as the vibration of the bonds would be different, resulting in a different IR spectrum. Two common advantages of the IRD are differentiating cocaine base from cocaine hydrochloride and methamphetamine from phentermine, something that is not possible on normal GC/MS runs. The disadvantage of the IRD is that a pure or nearly pure sample is required. As discussed earlier, this is not the normal case as most drugs are cut or contaminated due to poor manufacturing practices.

CONCLUSIONS

Treatment of patients presenting after using bath salts should be focused on reducing agitation and psychosis and supporting renal perfusion. The majority of successfully treated cases have used benzodiazepines and antipsychotics along with general supportive care (29,51,52). Although many of these patients will have excited delirium, it is important that the clinician strives to achieve chemical rather than physical restraint. The use of physical restraints has been associated with sudden death in persons with stimulant-induced psychosis (64).

Combining the worst of both methamphetamine and MDMA, bath salts are dangerous drugs and clinicians need to be aware of their clinical effects as well as their addictive and psychiatric manifestations. Their use should be suspected in any young adult presenting with new-onset psychosis, renal failure, or manifesting sympathomimetic symptoms and agitated delirium.

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ARTICLE SUMMARY

1. Why is this topic important?

During the past several years, emergency physicians have seen a growing number of bath salt abuse cases. Currently, there is a lack of concise information on the pharmacology, toxicology, and clinical management of these patients.

2. What does this review attempt to show?

This review attempt to show how differences in the chemistry between the different bath salts influences the pharmacology and toxicology. The pharmacology and toxicology is also used as the basis for the clinical management of patients exposed to bath salts.

3. What are the key findings?

This review discusses the pharmacology, toxicology, and chemistry of previously and recently identified synthetic cathinones.

4. How is patient care impacted?

Patient care is impacted by increasing the knowledge of emergency physicians of bath salts. In addition, the pharmacological basis for treating patients is discussed in order to assist emergency physicians in treating their patients.