# Manifestations and treatment of central nervous system complications associated with synthetic cathinone ("bath salts") toxicities

Ryan R. Gries, Doctor of Pharmacy Candidate 2014[1]
Kristyn Straw, PharmD, BCPP[2]

[1]College of Pharmacy Glendale, Midwestern University
[2]Southern Arizona VA Health Care System
Tucson, AZ

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## INTRODUCTION

"Bath Salts" or synthetic cathinone derivatives have made waves during the past several years in the designer drug market as a new trend in drugs of abuse. Natural cathinones are psychoactive chemicals that have been historically consumed by chewing Khat, or ***Catha edulis***, leaves and shoots in regions of Africa and the Arabian Peninsula. Traditionally, Khat has been utilized to increase alertness and enhance euphoria as CNS stimulants commonly used by religious leaders and militant factions.[1,2] The pharmacologic effects of synthetic cathinones have been noted to be similar to cocaine, amphetamines, and 3,4-methylenedioxy-N-methylamphetamine (MDMA/ecstasy) although each have their own unique profile. There are at least 12 different known synthetic cathinones that are currently available but 4-methylmethcathinone (mephedrone), 3,4-methylenedioxypyrovalerone (MDPV), and 3,4-methylenedioxymethcathinone (methylone) are three of the more common analogues.[1] The DEA added mephedrone, methylone and MDPV to the list of Schedule 1 substances as part of the Control Substances Act in September 2011.[3-5] This was an emergency scheduling and has not yet been made permanent. The other 9+ synthetic cathinones remain unscheduled.

These designer drugs are sold online and in "head" or smoke shops and are commonly packaged in trendy packets with catchy names such as "Ivory Wave", "Purple Wave", "Red Dove", "Blue Silk", "Cloud Nine", and "White Lightning".[1,6,7] They are generally sold as a white power under the disguise of "plant food," "bath salts," or "insect repellant" and are commonly labeled "not for human consumption".[1,7,8] Some of the containers hold up to 500 milligrams with a low dose being between 3–5 mg and a typical dose around 5-20 mg.[3,4,7] A few case reports have noted individuals consuming upwards of 2-3 grams prior to hospital admission.[9,10] Many routes of administration have been reported including nasal insufflation, ingestion, rectal insertion, inhalation, inhalation of smoke, intravenous (IV) injection, and gingival application.[1,7,8]

There have been no long term studies looking into the adverse effects of these substances; therefore, health and safety risks of consumption, especially among chronic abuses, are unknown. Many adverse events, including several deaths, have been attributed to the consumption of synthetic cathinones.[11,12] Individuals generally present with a sympathomimetic toxidrome that is similar to that of other stimulants such as methamphetamine.[1] It has been noted that several users show signs of serotonin syndrome, delirium, and drug-induced psychosis as well.[3,13,14] There are no evidence based studies that have looked in to the treatment or management of the many overdose cases that have presented to the emergency departments in recent years. Currently treatment practices have largely been supportive in nature.[3] The goal of this article is to look into these reported practices, and noted considerations, in an attempt to help streamline therapy for the psychiatric and neurologic issues that arise during the treatment of patients who have consumed, or are suspected of consuming, synthetic cathinone derivatives.

## PHARMACOLOGY/TOXICOLOGY

Synthetic cathinones are phenethylamine derivatives and, as such, are β-keto analogues of amphetamine.[1,15] These chemicals are known to promote the release of the neurotransmitters serotonin, dopamine, and norepinephrine as well as partially inhibit their re-uptake.[1,4,16] This is the mechanism that causes the sympathomimetic toxidrome that typically includes tachycardia, hypertension, tachypnea, and shortness of breath. The CNS effects include, but are not limited to, hyperreflexia, tremor, hyperarousal, agitation, paranoia, seizures, coma, and mydriasis.[1] Diaphoresis,

hyperthermia, hallucinations, and hyponatremia may be present and could very well be symptoms of cathinone-induced serotonin syndrome.[13,14] Drug-induced psychoses are often a concern in dealing with patients who are known to have taken these substances. Mephedrone has been shown to have dopamine releasing capabilities that are higher than MDMA and approach that of methamphetamine, suggesting its addiction potential may be aligned closer to methamphetamine.[17]

As previously mentioned, doses are known to range from a low end of 3-5 mg to an upper range of several grams. This makes manifestations and treatment more difficult when patients may present with such a range of ingestion (1,000-fold differences). Although there is not much information on the pharmacology of this class as a whole, the generic timeline of experience for one dose is approximately 1.5 hours for onset, 3-4 hours for duration and approximately another hour for coming down; total experience around 6-8 hours. Confirmed blood levels of MDPV have ranged from 0.016 mg/L to 8.0 mg/L and urine levels from 0.04 mg/L to 3.8 mg/L.[4,18] One report mentioned five confirmed, postmortem blood levels of mephedrone between 0.13 mg/L and 5.1 mg/L.[6]

Gas Chromatography and Mass Spectrometer tests for certain synthetic cathinones are available.[12] Assay tests have been developed to screen for various synthetic cathinones but are not yet frequently part of the routine toxicology screens.[4,7,19] Therefore, synthetic cathinones often go undetected. To further complicate matters, synthetic cathinones can sometimes result in false positives for phencyclidine (PCP) making the situation even murkier.[3,20]

## MANIFESTATIONS OF INTOXICATION

Patients intoxicated with cathinones tend to exhibit aggressive, violent behavior and are often suffering from auditory and visual hallucinations, tremors, severe anxiety as well as paranoia. Synthetic cathinone intoxication should be considered in cases where a patient is exhibiting agitated delirium with no clear etiology.[21] One report noted that 49% of suspected users suffered from psychiatric complications and 91% suffered from neurologic defects.[1] Another study found that 78% of patients being treated for intoxication were male and 69% had a history of illicit drug use. These patients were also found to be prone to have frequent re-admissions.[3]

Joksovic mentioned in his case report that mephedrone, in particular, raised serotonin levels 950% which is a 10-fold increase over the effects of amphetamines. This may explain the increasing potential of synthetic cathinone users to present with some of the common signs and symptoms of serotonin toxicity such as acute delirium, autonomic excess, hyperreflexia and hallucinations.[13] These instances of acute delirium have been labeled "excited delirium" or "toxic delirium" similar to that of cocaine, methamphetamine, and MDMA, and this may be caused by the underlying serotonin toxicity.[3,14] Hyponatremia is associated with serotonin syndrome and has been mentioned in several case reports (including two where the patients died) and could very well be the cause of the delirium.[10,12] It has been suggested that there may be a similar mechanism as is involved in MDMA-associated hyponatremia.[8]

Although frequently the signs and symptoms of toxicity resolved shortly after the autonomic storm passes, several instances have been reported of psychosis persisting for weeks after overdose.[14] Lack of memory, sometimes persisting for a couple of weeks, is another chief complaint that several of cathinone users have mentioned.[4,10,11,16] It has been suggested that this may be due to drug-induced delirium as opposed to psychosis.[11] Hallucinations may also be attributed to delirium.

## PHARMACOLOGICAL TREATMENT

The overall care of patients suspected of suffering from cathinone intoxication is one of a supportive nature.[4,7,8,20] Treatment largely consists of managing the symptoms of autonomic excess which include hyperthermia and dehydration that may develop into rhabdomyolysis.[3] Electrolyte levels, blood glucose, and blood pressure should be carefully monitored and treated appropriately. Since aggressive and bizarre behavior is not unusual, judicious use of restraints has been suggested.[4] It is important to emphasize that no two cases should be handled quite the same and medical practitioners should do their best to individualize the treatment regimen.[1]

Since patients suffering from cathinone toxicity are prone to aggressive and violent behavior, gaining adequate control of the agitated person is key. Treatment should not be delayed for confirmatory laboratory results.[21] Use of benzodiazepines is the reported first line therapy for agitation, aggression, and psychosis.[1,4,7,8,21,22] The majority of case reports that described use of pharmacological treatments used chose lorazepam either IV or IM and a starting dose between 2 mg and 10 mg.[10,13,23] Lorazepam would seem to be an ideal agent considering its manageable onset of action as well as its duration of action. However, diazepam and midazolam may also be utilized in certain situations that require a quicker onset. Frequent re-dosing is often necessary.

Experts agree on the approximate starting doses of the commonly used benzodiazepines (2 mg for lorazepam and 10 mg for diazepam) but differ on the how quickly these should be re-dosed (Arnold and Ryan state every 3 – 5 minutes as necessary, up to hundreds of milligrams if needed, while Mas-Morey and colleagues take a more conservative approach with every 2 hours).[1,21] If symptoms of agitation and aggression persist and treatment with benzodiazepines fails to bring the patient into an adequate level of sedation, temporary use of an antipsychotic may be warranted.[1,21]

Aggressive use of antipsychotic medications in patients suffering from cathinone toxicity is cautioned, however.[3] Butyrophenones, such as haloperidol, and second generation antipsychotic medications, like risperidone and ziprasidone, have been implicated in lowering the seizure threshold and causing arrhythmias as well as hyperthermia.[1,4,21,22] Haloperidol 5 mg IV infused slowly over 1 – 2 minutes or risperidone 1 mg by mouth have been suggested as advised initial therapy.[1] It should be noted; however, that no controlled studies have been conducted looking into their safety or efficacy in this population.[21]

In one patient case report, a female who presented with cathinone induced psychosis received 2 mg lorazepam IM initially and was re-dosed every 2-4 hours along with haloperidol 1 mg every 4 hours. By day 2 the patient's paranoia and sleep patterns improved and on day 4 she was released following complete resolution of her psychotic symptoms.[13] Another such case of cathinone induced psychosis occurred where the patient, a 38 year old male, initially received lorazepam 3 mg IV infusion over 3 hours and needed a total of another 10 mg lorazepam along with 5 mg haloperidol IM in order to be appropriately sedated. His psychosis also resolved completely and he was discharged after a three day hospitalization.[10] Three separate cases reported success in dosing psychotic patients with 0.5 mg risperidone by mouth twice a day with marked improvements over the following 24 hours. All these patients were discharged home after a 3-5 day stay without need for continued medications.[10,11]

Benzodiazepines also serve well as first line agents to combat amphetamine-like, drug-induced seizures. The use of phenytoin should be avoided in patients with intoxication-induced seizures since the mechanism of action for phenytoin is to isolate seizure focus and it does not treat the underlying imbalance of neurotransmitters which are responsible for these drug-induced seizure types.[1]

If a patient is still resistant to treatment and has been admitted to the Intensive Care Unit, it has been suggested to start IV propofol in order to reach appropriate sedation until the autonomic storm starts to pass.[1,6]

## SPECIAL CONSIDERATIONS

There are many considerations and situations that have been previously mentioned in published literature that could impact the chosen course of treatment for some of these patients. One such problem is the lack of knowing what, or how much a patient has consumed, especially without the use of routine drug testing and accompanied reference levels. Another similar problem is that there is frequently multi-drug intoxication complicating the patient's presentation and therefore potential treatment.[22] Not surprisingly, ethanol, cocaine, MDMA, methamphetamine, ketamine, cannabis, nitrites, benzodiazepines, opiates, zolpidem, gamma-hydroxybutyrate, and diphenhydramine have all been detected at the same time as confirmed cases of synthetic cathinone use.[6,12]

Many of these patients may also have psychiatric comorbidities such as underlying substance use issues, depression, or schizophrenia.[20,24] These patients may be concurrently prescribed psychiatric medications that could be attributing to the severity of their condition such as an antidepressant that could increase their likelihood of developing serotonin toxicity.[7,20] It may be recommended, if synthetic cathinone use is suspected, to change underlying therapies. One such case study found success in treating comorbid depression and cathinone dependence using bupropion, a cathinone-derivative and anti-depressant medication which inhibits the reuptake of dopamine and norepinephrine.[9]

## CONCLUSION

Synthetic cathinones have made their mark on the designer drug scene. Legislation has been passed rendering several of these compounds illegal; however, this has not eliminated the presentation of patients with the signs and symptoms of cathinone toxicity. Treatment is mostly supportive in nature. Benzodiazepines, particularly lorazepam and diazepam, are first line therapies for agitation, aggression, psychosis, and seizures. Antipsychotic medications have been used but this practice should be approached with extreme caution due to potential exacerbation of hyperthermia, arrhythmias and seizures. The entire patient profile should be considered and therapy, both during and post-intoxication, should be individualized.

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