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REVIEW

Synthetic cathinone abuse

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Abstract: The abuse of synthetic cathinones, widely known as bath salts, has been increasing since the mid-2000s. These substances are derivatives of the naturally occurring compound cathinone, which is the primary psychoactive component of khat. The toxicity of synthetic cathinones includes significant sympathomimetic effects, as well as psychosis, agitation, aggression, and sometimes violent and bizarre behavior. Mephedrone and methylenedioxypyrovalerone are currently the predominantly abused synthetic cathinones.

Keywords: designer drugs/chemistry, street drugs/pharmacology, substance-related disorders/epidemiology, alkaloids/poisoning

Introduction

A recent manifestation of the interaction between substance abusers, those seeking to profit by providing substances of abuse, and the desire of both parties to avoid legal censure, is the emergence of bath-salt abuse. Bath salts in this context refer to several synthetic cathinones sold as either bath salts or plant food, but not intended for any horticultural or personal hygiene use. Despite the ubiquitous packaging disclaimer "not intended for human consumption," these substances are sold as "legal highs" and drugs of abuse.[1]

History

Cathinone is a naturally occurring phenylalkylamine which is found in the leaves of khat (*Catha edulis*), a shrub or small tree indigenous to East Africa and the Arabian Peninsula.[2] Historical references to the chewing of khat leaves for their euphoric and stimulant effects dates back many centuries, and today this practice is prevalent in such countries as Somalia, Yemen, Kenya, and Ethiopia.[3] Khat leaves contain multiple compounds, notably phenylalkylamine alkaloids that include norpseudoephedrine, cathinone, and cathine.[4] Studies in the 1930s to determine the psychoactive components of khat initially erroneously identified norpseudoephedrine as the main psychoactive compound.[4] In 1975, cathinone was isolated from khat leaves and determined to be its principal psychoactive component.[5] Although cathinone is a chiral molecule, khat leaves contain only the *S* (–) enantiomer,[6] and synthesis of the racemate was not achieved until 1982.[7] Cathinone begins to decompose shortly after leaves are harvested, and thus fresh leaves are sought for chewing. This may explain why khat chewing has largely remained limited to geographic regions where *Catha edulis* grows.[3] In distinction to synthetic cathinone abuse, habitual khat chewing reportedly results

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in only mild psychological dependence and mild withdrawal symptoms.[8,9]

As reviewed by Kelly, the earliest report of synthetic cathinone synthesis is in 1928 with the synthesis of methcathinone in Germany, followed by the synthesis of mephedrone in 1929.[10] Today, there are approximately 30 known synthetic cathinones.[10]

Although many synthetic cathinones have been investigated as anorectics, central nervous system stimulants, and antidepressants, clinical utility has been hindered by problems with abuse and dependence. For instance, methcathinone was initially used as an antidepressant in the USSR but removed from clinical use due to abuse.[11] Currently, the synthetic cathinone diethylpropion is available for use as an anorectic, but is infrequently prescribed due to abuse and dependence. In addition, diethylpropion has been shown to be neurotoxic in animal studies.[12] Pyrovalerone has been used in the past for chronic fatigue,[13] while the most clinically successful cathinone is bupropion, which is widely prescribed for depression and smoking cessation.[14]

Patterns of abuse

Large-scale abuse of synthetic cathinones began with the use of methcathinone in the USSR in the 1970s and 1980s.[11] Clandestine methcathinone manufacture first appeared in the US in Michigan in 1991, followed by significant problems of abuse in the early 1990s.[11]

Since 2004, abuse of various synthetic cathinones has been reported in Asia, Israel, the EU, and the US, possibly fueled by a decrease in purity and availability of other stimulant drugs of abuse, including MDMA (3,4-methylenedioxy-*N*-methylamphetamine) and cocaine.[15] Data regarding synthetic cathinones seized in the EU since 2006 reveals ten different substances, including mephedrone, methylone, and MDPV (3,4-methylenedioxypyrovalerone), with mephedrone involved in 89% of seizures in the UK.[14] US Customs and Border Protection drug-seizure data report the seizure of multiple different synthetic cathinones between July 2009 and April 2011, including MDPV and mephedrone.[1] User surveys, poison center reports, and case series in the US and Europe indicate that current synthetic cathinone abuse involves primarily mephedrone and MDPV, with methylone, naphyrone, and flephedrone being less often implicated.[9,16–19]

Law-enforcement data indicate that synthetic cathinone supply frequently originates in the People's Republic of China, Pakistan, and India.[1] Substances are then sold to the public via the Internet and in retail establishments, including "head shops," gas stations, convenience stores, and skateboard shops. Products are labeled as bath salts, plant food/fertilizer, vacuum freshener, pond cleaner, and insect repellent, and are typically sold as tablets or white powders.[1] While oral ingestion and nasal insufflation have been reported as the most common means of use,[9,16] parenteral exposure has also been described, with a recent case series reporting injection as the most common means of use.[18]

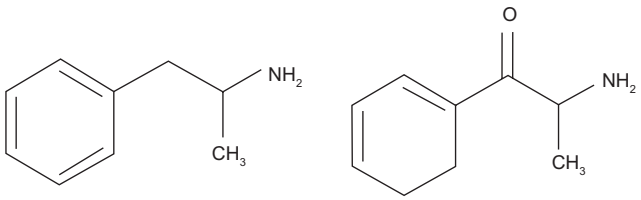
There is little epidemiologic data regarding synthetic cathinone use. Survey data imply that at least among certain demographic groups, use may be widespread. In a 2010 online survey sponsored by a magazine popular with UK clubbers, 41.7% of 2200 respondents reported having used mephedrone.[15,20] A 2010 survey of 1006 high school and university students in Scotland reported a 20.3% prevalence of mephedrone use.[9] Evidence from poison center calls and drug seizures in the US support the concept that synthetic cathinone abuse is a recent and increasing phenomenon. Synthetic cathinone-related calls to US poison centers increased from zero in 2009 to 304 in 2010 and 6138 in 2011.[16,21] Drug samples seized in the US and analyzed by state and local forensic laboratories reveal 34 reports of synthetic cathinones in 2009 and 628 in 2010.[17,22]

Coingestion of other drugs of abuse and alcohol frequently accompanies synthetic cathinone use.[19,23,24] While there are no data regarding people seeking treatment for synthetic cathinone dependence/addiction, users have reported a strong compulsion to redose, as well as addiction/dependence.[9]

The legal status of cathinone analogues continues to evolve as new substances are produced in order to evade existing laws.[1] Mephedrone and several other substituted cathinones were banned in the EU in 2010,[23] and as of July 2012, mephedrone, MDPV, and methylone have been added to Schedule I of the Controlled Substances Act in the US.[25]

Chemistry

As seen in Figure 1, cathinones are structurally related to amphetamines.[26] Both are substituted phenethylamines



Amphetamine Cathinone

Figure 1 Amphetamine and cathinone structures.

with cathinones possessing a ketone group at the β-carbon position. Figure 2 demonstrates the general structure of substituted cathinones. Various R-group substitutions give rise to the approximately 30 known cathinones, many of which have amphetamine analogues to which they are identical, save for the β-carbon ketone group.[26] Thus, replacing a hydrogen with a ketone converts amphetamine to cathinone, methamphetamine to methcathinone, and MDMA to methylone.[10] The structure of several cathinones recently implicated in recreational abuse can be seen in Figure 3.

Pharmacokinetics

At present, there is a scarcity of data concerning the pharmacokinetics of synthetic cathinones in humans. However, insights can be gleaned from animal data as well as inferred from studies of naturally occurring cathinones.

The pharmacokinetics of cathinone have been studied in humans by multiple investigators since the initial isolation of this compound from khat leaves in 1975.[4] After chewing khat leaves, absorption takes place primarily in the oral mucosa, with a secondary contribution from absorption in the stomach and small intestine.[27] Extraction of khat alkaloids by mastication has been reported to be very efficient;[27] however, chewing results in delayed peak plasma concentrations when compared to administering oral cathinone. Following chewing khat leaves, time to peak plasma concentrations of 138 ± 39 minutes[27] and 127 ± 30 minutes[28] have been reported, while administration of gelatin cathinone capsules produced peak plasma concentrations in 72 minutes.[29] Orally ingested cathinone undergoes extensive first-pass hepatic metabolism primarily to norpseudoephedrine with a smaller fraction converted to norephedrine.[2,27,29,30] Very little cathinone is excreted unchanged, with studies in humans reporting urinary excretion of unchanged cathinone to be between 2%[2] and 7%.[31]

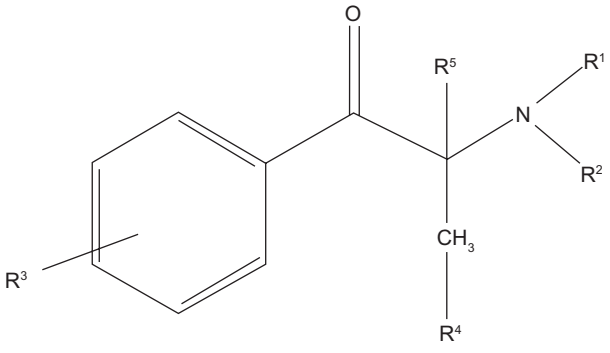


Figure 2 General cathinone derivative structure.

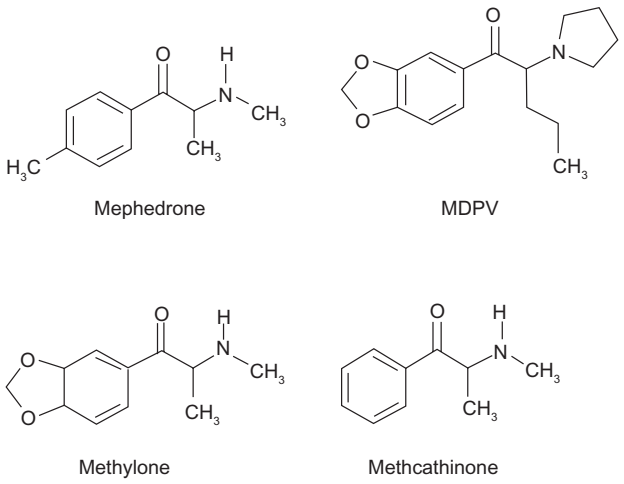


Figure 3 Selected substituted cathinone structures.
Abbreviation: MDPV, methylenedioxypyrovalerone.

The half-life of cathine is reported to be 5.2 ± 3.4 hours, and cathinone 1.5 ± 0.8 hours in humans.[32]

Research regarding synthetic cathinone pharmacokinetics in humans is lacking. There are no controlled studies of human in vivo synthetic cathinone pharmacokinetics; however, several studies examining urinary metabolites in people who claim to have ingested synthetic cathinones exist.[33–36] In vivo animal studies have been published,[33,35–37] as have in vitro investigations utilizing animal hepatocytes[38,39] and human liver microsomes.[36,37,40] Generalizing the findings of these studies is complicated not only by varying experimental models but also by the multiple different synthetic cathinones studied. However, within the framework of these limitations, several preliminary conclusions may be drawn. Similar to naturally occurring cathinone, synthetic cathinones appear to undergo extensive phase I and II metabolism,[33–38,40] with little of the drug excreted unchanged in urine.[35,37] Commonly identified phase I reactions are demethylation and oxidation, as well as reduction of the β-keto moiety.[35,36,38] Glucuronidation of metabolites has been described by several investigators.[37,38] Indirect evidence of sulfate conjugation has been reported;[33] however, other investigations have been unable to confirm this.[37,38] Human liver microsomes have been used by Meyer et al in two separate studies, with the finding that human cytochrome P450 (CYP) enzymes CYP2B6, CYP2C19, CYP2D6, and CYP1A2 are involved in synthetic cathinone metabolism.[36,37] While there are no studies examining synthetic cathinone half-lives in humans, surveys of users suggest that the duration of effects of mephedrone and MDPV are "short," with users reporting frequent redosing at 1- to 2-hour intervals and a duration of effects of approximately 2–4 hours.[41,42] This is not

inconsistent with findings in rat hepatocytes of a half-life of approximately 1 hour for mephedrone.[38]

Compared to amphetamines, the ketone group of cathinones confers a greater polarity and a predicted increased lipophilicity.[43] Thus, diffusion across the blood–brain barrier may be decreased.[43] However several pyrrolidine derivatives, including MDPV and MDPPP (3,4-methylenedioxy-α-pyrrolidinopropiophenone), have lower polarity and have shown high solubility in organic solvents.[15] In addition, recent in vitro studies of mephedrone, MDPV, methylone, ethylone, butylone, and naphyrone demonstrated high blood–brain barrier permeability of all these synthetic cathinones.[44]

Mechanism of action

In vitro studies utilizing human and animal cell preparations suggest that cathinones acutely increase extracellular dopamine, norepinephrine, and serotonin levels. Similar to amphetamines, cathinones inhibit dopamine, norepinephrine, and serotonin plasma membrane and vesicular monoamine transporters, resulting in increased neurotransmitter synaptic concentration.[45,46] Different cathinones display varying ability to cause increases in extracellular dopamine, norepinephrine, and serotonin levels, which may account for the different mood-altering effects, toxicity, and potential for addiction related to these compounds. Mephedrone, for instance, has been shown to significantly inhibit norepinephrine reuptake.[46] While the expected sympathomimetic effects have not been specifically demonstrated in human studies, case reports do support a strong sympathomimetic effect of some synthetic cathinones, including mephedrone.[18,24,47] The reported addictive potential of several synthetic cathinones is likely related to effects on increasing extracellular dopamine, as has been demonstrated in animal models.[48]

Toxicology

The current body of knowledge regarding the adverse effects of synthetic cathinones is based largely on case reports, data from poison centers, and surveys of users. Inherent flaws in these data are likely, as users may not be accurate regarding substances ingested, the amounts ingested, and the presence of coingestions. Compounding this is the limited ability to test accurately for synthetic cathinones,[15] and purchased products that do not contain the substances advertised or contain unlisted compounds in addition to the advertised drug. Inaccurate labeling of products has been reported, with products containing synthetic cathinones other than the listed compound, other substances of abuse, including MDMA and ketamine, and pharmaceuticals, including acetaminophen, caffeine, benzocaine, and lidocaine.[49,50] Additionally, products sold as cocaine and MDMA have been found to contain synthetic cathinones.[51,52] Finally, a review of 15 products sold as "legal highs" in the USA found no ingredients were listed on any of the packages, thus making it very difficult for patients to report exposures accurately.[19]

Toxicity of naturally occurring cathinones

The reported toxicity of the natural substances cathinone and cathine appears less severe than many of their synthetic counterparts. This may be due to chewing khat representing the primary means of ingestion and the bulk of leaves that must be chewed in order to produce significant toxic effects.[29] Described toxic effects of chewing khat include depression, irritability, insomnia, anorexia, and paranoid psychosis. Adverse cardiovascular effects include hypertension, tachycardia, and an increased incidence of acute myocardial infarction and cerebral vascular accidents.[53] Chewing khat is also associated with an increased incidence of oral cancer.[54]

Toxicity of synthetic cathinones

Toxic effects of synthetic cathinones include sympathomimetic effects, as well as psychological effects, including aggression, agitation, paranoia, and delusions.[16,19,55] Seizures, hyponatremia, hyperthermia, rhabdomyolysis, disseminated intravascular coagulation, renal failure, and hepatic failure have also been reported, as have several deaths.[19,47,56,57] Several reports, primarily from Eastern Europe, document parkinsonism in patients following long-term parenteral use of methcathinone. Manganese contamination of homemade methcathinone has been identified as the cause.[58,59]

Chronic amphetamine use is known to be neurotoxic to dopaminergic neurons, resulting in long-term reductions in brain dopamine concentrations in chronic users.[60] Serotonergic neurotoxicity as a result of MDMA use occurs in animals, and possibly humans.[61] Whether synthetic cathinone abuse is related to dopaminergic or serotonergic neurotoxicity in humans is unknown; however, serotonin neurotoxicity has been described with methylone and mephedrone in rats.[62]

User-reported adverse effects

User-reported adverse effects of synthetic cathinone use commonly include agitation, paranoia, bruxism, palpitations, headache, and depression.[9,63,64] A 2010 survey of 1006 students in Scotland with 205 mephedrone users found 56% reported at least one adverse effect, most commonly bruxism (28.3%) and paranoia (24.9%).[9]

Table 1 Synthetic cathinone toxicity: case reports with ≥15 patients without analytical confirmation of synthetic cathinone exposure

Study	Patients	Reported exposure	Percent reporting							
			Agitation	Tachycardia	HTN	Seizure	Chest pain	Hyperpyrexia	Elevated CK	Low sodium
CDC[1]	35	MDPV, "bath salts"	66	63	23	29	a	a	2.9	a
Dargan et al[23]	72	Mephedrone	38.9	36.1	13.9	6.9	12.5	0	13.8[b]	1.4
Regan et al[24]	57	Mephedrone	40.4	79	74	3.5	24.6	d	33.3[c]	a
Wood et al[47]	15	Mephedrone	53.3	40	20	20	b	a	a	a

Notes: [a]Not reported; [b]CK measured in 18 patients, elevated in ten; [c]CK measured in 20 patients, elevated in 19; [d]individual data not given. Temperature range of all patients 34.8°C–38.8°C.

Abbreviations: CK, creatine kinase; HTN, hypertension; MDPV, methylenedioxypyrovalerone; CDC, Centers for Disease Control and Prevention.

Mixmag is a publication popular with UK clubbers and host of the large Mixmag Drugs Survey, which in 2012 included online responses from over 15,500 respondents. Commonly reported adverse mephedrone effects included depression (41%), agitation (23%), "overheating" (26%), severe headache (12%), and chest pain (10%).[63] In a smaller study from Ireland utilizing privileged-access interviewing of eleven intravenous users of mephedrone, all users reported intense paranoia, and two reported extreme aggression and violence.[64]

Adverse effects reported to poison centers

Calls by physicians to the National Poisons Information Service in the UK from March 2009 to February 2010 included 188 calls regarding cathinones, with 131 of these concerning mephedrone. Reported adverse effects included agitation or aggression (24%), tachycardia (22%), confusion or psychosis (14%), chest pain (13%), and palpitations (11%).[16] A report documenting synthetic cathinone-related calls to Texas poison centers in 2010 and 2011 found 362 calls, with common adverse effects being tachycardia (45.9%), agitation (39.2%), hypertension (21.0%), and hallucinations (17.7%).[55] During an 8-month period in 2010 and 2011, 236 calls were received by poison centers in Kentucky and Louisiana regarding synthetic cathinone intoxication. Commonly reported toxicities included agitation (82%), combative behavior (57%), tachycardia (56%), hallucinations (40%), and paranoia (36%). This study also included descriptions of severe delusional behavior, including leaving a 2-year-old child in a highway "because she had demons," firing guns at nonexistent people and "demons," and destroying all the windows in a home and walking barefoot through the resulting broken glass. One patient died as a result of a self-inflicted gunshot wound while delusional.[19]

Adverse effects reported in case series

Multiple case reports from emergency departments concerning patients presenting with synthetic cathinone toxicity, without analytical confirmation of substances ingested, have been published. Findings are summarized in Table 1.

Case reports in which the presence of synthetic cathinones was confirmed by body-fluid or tissue analysis include multiple single-patient case reports, a series of three deaths involving methylone, and a series of seven patients with mephedrone toxicity.[17,51,56,57,65–70] A series of 13 patients with confirmed MDPV intoxication has been published, but clinical findings in patients with confirmed and unconfirmed exposures are grouped together.[19] In the report of seven patients with confirmed mephedrone ingestion, five of the patients had only synthetic cathinones detected on drug screening, while the other two patients also tested positive for cocaine. Adverse effects included heart rate >100 (five patients), systolic blood pressure >160 (three), agitation (four), and seizure (one). One patient had hyponatremia with a serum sodium concentration of 125 mmol/L, and one patient had rhabdomyolysis. No patients had significant hyperpyrexia.[65] In the three reported deaths from methylone intoxication, all patients had hyperpyrexia and seizures, with metabolic acidosis, disseminated intravascular coagulation, and acute renal failure also reported.[66] Single-patient case reports have also reported hyperpyrexia, seizures, hyponatremia, rhabdomyolysis, and metabolic acidosis.[51,56,57,69]

Conclusion

The recreational use of synthetic cathinones, widely known as bath salts, has been the subject of much recent interest. Synthetic cathinones are derivatives of the naturally occurring compound cathinone, which is the primary psychoactive component of khat. Cathinones are structurally related to amphetamines, and their mechanisms of action are thought

to be similar. Although the first synthetic cathinones were synthesized in the 1920s, and recreational abuse can be traced back many decades, rapid increase in use began in the mid-2000s, likely fueled by the legality of these substances. Mephedrone and MDPV have been the dominant synthetic cathinones of abuse in recent years, and are implicated in an increasing number of emergency department visits due to adverse effects. Case series and poison center data indicate that toxicity includes significant sympathomimetic effects, as well as psychosis, agitation, aggression, and sometimes violent and bizarre behavior. Multiple deaths attributed to synthetic cathinone use have been reported. There is a paucity of data concerning the pharmacodynamics and pharmacokinetics of synthetic cathinones in humans, with current understanding based primarily on in vitro and animal studies. Long-term effects of synthetic cathinone use, including the potential for addiction/dependence, are largely unknown. Although mephedrone and MVPV are now illegal in many countries, the current landscape of synthetic cathinone abuse will likely continue to shift as new substances are developed and marketed, and as legal pressures change.

Disclosure

The author reports no conflicts of interest in this work.

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