Toxicology Letters 211 (2012) 144–149

Contents lists available at SciVerse ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Mini review

Synthetic cathinones: Chemistry, pharmacology and toxicology of a new class of designer drugs of abuse marketed as "bath salts" or "plant food"

M. Coppola[a,*], R. Mondola[b]

[a] Department of Addiction, ASL CN2, Viale Coppino 46, 12051 Alba (CN), Italy
[b] Department of Mental Health, ASL CN1, Via Torino 70/B, 12037 Saluzzo (CN), Italy

ARTICLE INFO

Article history:
Received 29 January 2012
Received in revised form 10 March 2012
Accepted 12 March 2012
Available online 21 March 2012

Keywords:
Synthetic cathinone
MDPV
Mephedrone
Bath salts
Designer drug

ABSTRACT

In 2000s, many synthetic cathinones have received a renewed popularity as designer drugs of abuse, particularly among young people. Despite being marketed as "bath salts" or "plant food" and labeled "not for human consumption", people utilize these substances for their amphetamine or cocaine like effects. Since the time of their appearance in the recreational drug market, in several countries have been signaled numerous confirmed cases of abuse, dependence, severe intoxication and deaths related to the consumption of synthetic cathinones. The aim of this paper is to summarize the clinical, pharmacological and toxicological information about this new class of designer drugs of abuse.

Contents

* Corresponding author. Tel.: +39 0173316210; fax: +39 0173420344.
E-mail address: coppolamail@alice.it (M. Coppola).

0378-4274/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.toxlet.2012.03.009

1. Introduction

The first synthetic cathinones, methcathinone and mephedrone, were synthesized in the late 1920s, and since then, many other molecules have been produced. However, most of them have not been used for therapeutic purposes as a result of serious side effects. In 2000s, many synthetic cathinones have received a renewed popularity as designer drugs of abuse, particularly among young people (Brandt et al., 2010). These compounds, derived from the vegetable cathinone, molecule naturally present in the Khat plant (*Catha edulis*), are marketed as "bath salts" or "plant food" and labeled "not for human consumption" to circumvent the legislation on drugs of abuse (Kelly, 2011). Synthetic cathinones are sold in specialized shops known as "head shops" and in online shops, in particular, the internet market has contributed significantly to the spread of these substances (Schifano et al., 2010). Although they are often considered "legal highs", in fact their legal status is variable in different Countries and rapidly changing. In this regard, an important consideration is that the online market is able to respond quickly to changes in the legal status of recreational drugs offering for sale new legal alternatives (Walsh, 2011). Like cocaine or amphetamines, these substances are able to produce stimulant effects and are used in substitution of the traditional illicit drugs (Karila and Reynaud, 2011). Synthetic cathinones are a new trend in the recreational drug market and the paucity of human toxicological data combined with the numerous cases of abuse, dependence, severe intoxication and deaths drug related signaled in several Countries has generated concern in the international scientific community (Spiller et al., 2011). The aim of this paper is to summarize the clinical, pharmacological and toxicological information currently available about this new class of designer drugs of abuse.

2. Methods

In order to conduct a research of articles as extensively as possible, literature searches were performed using the following electronic databases: PubMed, Embase, PsycINFO, Cochrane database. The keywords used were: synthetic cathinones, mephedrone, 3,4-methylenedioxypyrovalerone, MDPV, pyrovalerone, methylone, methedrone, dimethylcathinone, ethylone, ethcathinone, 3-fluoromethcathinone, 4-fluoromethcathinone, butylone, khat, legal highs, plant food, bath salts, club drugs, meow meow, miaow miaow, new cocaine. Key words were used singly and in combination. In addition, the history of this new trend, patterns of use, subjective experiences and risk perception of users were reconstructed and analyzed using the information present within the unconventional references such as web communities, drug forum, mailing lists, chat rooms and e-newsletters. No restriction in language was used in our research.

3. Natural cathinones

3.1. Chemistry

Vegetable cathinones are phenylalkylamine alkaloids naturally present in the khat plant (*Catha edulis*), an evergreen slow-growing shrub or tree native to Ethiopia and cultivated in East Africa and South West Arabian Peninsula (Hassan et al., 2007). The main natural cathinones present in the khat are cathinone and cathine. Cathinone, the most abundant and powerful, is a beta-keto analog of amphetamine with a molecular weight of 149.19 g/mol (Kalix, 1992). This molecule, formally named *S*-(−)-2-amino-1-phenylpropan-1-one, is more labile in the presence of oxygen and it is oxidized and decomposed within a few days of harvesting or if dried (Griffiths et al., 1997). The stored product loses activity rapidly, becoming physiologically inactive after about 36 h. It is for this reason that for maximum power, khat should be picked in the morning and chewed in the afternoon (Baron, 1999). Cathine, formally named 1*S*,2*S*-norpseudoephedrine, arises from the metabolism of cathinone in the mature plant. This compound, molecular weight of 151.21 g/mol, is one of the optical isomers of phenylpropanolamine producing amphetamine-like effect less potent than cathinone (Schorno and Steinegger, 1979).

3.2. Pharmacology

Like amphetamines, cathine and cathinone are central nervous system (CNS) stimulants, but their potency is less. These alkaloids cause the release of catecholamines from pre-synaptic storage sites in the central and peripheral nervous system (Kalix, 1986; Schechter, 1990). In addition, these molecules may also have monoamine oxidase inhibition effects (Nencini et al., 1984). The psychotropic effects of khat start after about 1 h of chewing and they last for approximately 3 h (Kalix, 1996). Peak plasma levels of cathinone are obtained 1.5–3.5 h after the onset of chewing while it is barely detectable after 8 h. First-pass metabolism of cathinone in the liver leads to the formation of norephedrine. Only 2% of cathinone is excreted unmodified in the urine. The elimination half-life of cathine and cathinone are 5.2 ± 3.4 and 1.5 ± 0.8 h respectively (Kalix, 1990).

3.3. Toxicology

Clinical data have shown that cathine and cathinone determine an increase in blood pressure and heart rate, euphoria, alertness and psychomotor hyperactivity (Brenneisen et al., 1990). Several studies have shown that the chronic use of this plant may produce various harmful effects such as increased incidence of acute coronary vasospasm and myocardial infarction, esophagitis, gastritis, oral keratotic lesions and liver toxicity (Al-Halbori, 2005). Furthermore, insomnia, depression, anorexia, psychosis and impaired working memory have been reported after occasional or chronic use of khat (Balint et al., 2009; Colzato et al., 2011). In particular, khat use can exacerbate psychotic symptoms in people with pre-existing psychosis and precipitate psychotic disorders in vulnerable subjects (Yousef et al., 1995). Literature data suggest that khat use may induce abuse, tolerance and dependence. Despite khat induced dependence seems to be less likely than amphetamine or cocaine induced dependence, khat alkaloids have the potential to induce addiction disorders (Halbach, 1972). Khat induced tolerance appear to be more rapid than to that of amphetamines and there is a cross-tolerance between amphetamines and cathinone (Foltin and Schuster, 1982). Finally, it was reported a withdrawal syndrome after suspension characterized by insomnia, lack of concentration, craving, nightmares and slight trembling (Al-Halbori, 2005).

4. Synthetic cathinones

4.1. Chemistry

Synthetic cathinones are the beta-keto analogs of the natural cathinone, one of the psychoactive compounds present in khat plant. Most of the synthetic cathinones appeared in the recreational drug market since the mid-2000s are a ring-substituted cathinone closely related to phenethylamine family, differing only by a keto functional group attached at the beta carbon on the amino alkyl chain linked to the phenyl ring (Zaitus et al., 2009). Like phenethylamines, these compounds can exist in two stereoisomeric forms, which may have different potencies and it is likely that most ring-substituted derivatives are

racemic mixtures. It is also believed that racemisation of all synthetic cathinones can happen across keto–enol tautomerism. Cathinone is unstable and transforms to a dimmer (3,6-dimethyl-2,5-diphenylpyrazine) at room temperature. Synthetic cathinones can also reorganize via a dihydropyrazine dimer to form so-called "isocathinones". These molecules are either N-acylated or the nitrogen atom is part of a pyrrolidine ring, and most are produced as hydrochloride salts (Gibbons and Zloh, 2010). Except for pyrrolidine derivatives, they are generally less lipophilic and less able to cross the blood–brain barrier and consequently, less potent than phenylethylamine analogs. Pyrrolidine derivatives such as 3,4-methylenedioxypyrovalerone (MDPV) and 3,4-methylenedioxy-alpha-pyrrolidinopropriophenone (MDPPP) are a highly lipophilic subgroup of cathinone derivatives sharing the same skeleton of pyrovalerone. In particular, MDPV includes in its chemical structure a nitrogen atom attached to three carbon atoms composing a tertiary amino group that is responsible of the high solubility of this compound in organic solvents (Gibbons and Zloh, 2010; Dargan et al., 2011; justice.gov, 2012a,b; caymanchem/10624, 2012). Synthetic cathinones are generally encountered as white or brown amorphous or crystalline powders, occasionally encapsulated, while the tablets are less common (Gibbons and Zloh, 2010; Dargan et al., 2011; justice.gov/synthetic cathinones, 2011).

4.2. Pharmacology

There are very little data about the human pharmacokinetics and pharmacodynamics of cathinone derivatives. Like amphetamines, synthetic cathinones exert their stimulant effects via increasing synaptic concentration of catecholamines such as dopamine, serotonin and norepinephrine. These molecules are able to inhibit monoamine uptake transporters producing a decreased clearance of the neurotransmitters from the synapse. Furthermore, they may cause release of biogenic amines from intracellular stores (Cozzi et al., 1999). In rat study has shown that the activities of two neurotransmitter biosynthetic enzymes, tyrosine hydroxylase and tryptophan hydroxylase, are decreased following methcathinone administration, leading to reductions in the concentrations of dopamine and serotonin and their respectively metabolites in frontal cortex, hippocampus and neostriatum (Gygi et al., 1996). Synthetic cathinones are generally less able than amphetamines to cross the blood–brain barrier because the beta-keto group causes an increase in polarity. Unlike other synthetic cathinones, pyrrolidine derivatives have a higher ability to cross the blood–brain barrier because the pyrrolidine ring confers a low polarity to these molecules. The studies on the metabolism of synthetic cathinones have shown that they are N-demethylated the keto group is reduced to hydroxyl and ring alkyl groups are oxidised (Meyer and Maurer, 2010). The primary metabolism of methylone, ethylone and butylone starts with demethylation of the methylenedioxy ring, followed by O-methylation into 4-hydroxy-3-methoxy or 3-hydroxy-4-methoxymethcathinone mediated by catechol-O-methyltransferase. These metabolites are partially conjugated with glucuronides and sulfates and excreted in the urine together with unmetabolized molecules. N-dealkylation appears to be a minor pathway for the metabolism of these molecules (Zaitus et al., 2009). Mephedrone is N-demethylated to a primary amine, subsequently, ketone moieties are reduced to alcohols, finally, totyl group is oxidized to the corresponding alcohol. Some of the alcohols are conjugated with glucuronides and sulfates and excreted in the urine (Meyer et al., 2010). The metabolism of MDPV was evaluated in vitro using human liver microsomes and S9 cellular fractions for CY450 phase I and uridine 5-diphosphoglucuronosyltransferase and sulfotransferase for the phase II metabolism. This study has demonstrated that the main metabolites of MDPV are catechol and methyl-catechol pyrovalerone which are in turn sulfated and glucuronated (Strano-Rossi et al., 2011).

4.3. Toxicology

Synthetic cathinones have received large popularity, particularly among young people, for their cocaine and amphetamines like effects. In particular, the stimulant effects of these drugs have been compared to methylphenidate, at low doses, and cocaine or amphetamines, at high doses (scribd, 2012). The information currently available about the short and long-term human toxicological effects of these designer drugs of abuse are very limited. Desired effects reported by users include: increased sociability, energy, libido sexual performance and capacity of work, limited euphoria, empathy (Winstock et al., 2011; drugrecognitionexpert, 2012). Users also reported untoward effects such as: prolonged panic attack, tremor, agitation, insomnia, nausea, headache, tinnitus, vertigo, muscle twitching, dizziness, increased heart rate, altered vision, confusion, short-term memory difficulty, anhedonia, depression, suicidal thoughts, psychosis, tolerance and dependence (Winstock et al., 2010; drugs-forum, 2012; erowid, 2012). In literature have been reported several cases of severe acute toxicity and deaths related to the consumption of synthetic cathinones (acep, 2012; Wood et al., 2010; Gustavsson and Escher, 2009). Acute toxicity mainly includes neurological, cardiovascular and psychopathological symptoms such as: psychomotor agitation, motor automatisms, parkinsonism, tremors, tachycardia, chest pain, S–T segment changes, hypertension, hyperthermia, mydriasis, dizziness, delusions, paranoid psychosis, depression, panic attacks, long term changes in cognition and emotional stability, rhabdomyolysis, abdominal pain, vomiting, kidney damage, hyponatremia, headache, cerebral edema and seizures (Borek and Holstege, 2012; Durham, 2011; CDC, 2011; Panders and Gestring, 2011; Regan et al., 2011). Recently, a case of MDPV induced serotonin syndrome has been reported. The patient was treated with benzodiazepines and cyproheptadine for 8 days with slow resolution of the symptomatology (Mugele et al., 2012). Patients with acute intoxication related to mephedrone assumption have also shown serious vasoconstriction in extremities, skin rashes, decoloration of the skin and bruxism (Durham, 2011; CDC, 2011; Panders and Gestring, 2011; Regan et al., 2011). The therapeutic treatment generally includes low or moderate doses of benzodiazepines to control agitation or seizures and antipsychotics or propofol to control severe agitation and psychotic symptoms. Hyperthermia should be treated with aggressive cooling and hyponatremia should be treated with hypertonic saline and water restriction (Spiller et al., 2011).

4.4. Fatalities

Fatal intoxication have been associated with various molecules such as mephedrone, MDPV, methedrone, butylone and methcathinone, but in many cases laboratory analysis revealed the presence of multiple drugs of abuse (Prosser and Nelson, 2012). In confirmed mephedrone related deaths, the postmortem blood concentration detected was between 0.13 and 22 mg/L, while in confirmed butylone related deaths the postmortem blood concentration detected was between 0.435 and 1.2 mg/L (Maskell et al., 2001; Torrance and Cooper, 2010; Carter et al., 2000). In a recent case of confirmed MDPV related death, the serum and urine concentration was 82 ng/mL and 670 ng/mL respectively (Murray et al., 2012).

4.5. Tolerance, dependence and withdrawal syndrome

Data currently available have shown that the frequent consumption of high doses of synthetic cathinones induces tolerance, dependence, craving and withdrawal syndrome after sudden

suspension (CDC, 2011; droganews, 2012). Although the typical doses range of MDPV appear to be between 5 and 30 mg in a single ingestion, some users reported tolerance with consumption of doses higher 200 mg in a single session (Coppola and Mondola, 2012). Several users have reported a withdrawal syndrome after abrupt cessation of long-term use of methcathinone, mephedrone and MDPV. This syndrome includes: depression, anergia, anhedonia, anxiety, sleep disorders fatigue and craving. Craving, anhedonia and anergia can last for several week (namsdl, 2012; CDC, 2011; Winstock et al., 2011).

4.6. Detection

Synthetic cathinones are not detected via standard drug test but it is required the gas chromatography/mass spectrometry or liquid chromatography/mass spectrometry (GS/MS). Immunoassay field tests for methamphetamines can give false positive reactions with some synthetic cathinones (Ojanpera et al., 2011; EMCDDA, 2012). In some cases, synthetic cathinones have been analyzed in human hair, in particular, in postmortem analysis the hair concentration detected for mephedrone and methedrone was between 4.2–4.7 ng/mL and 29–37 ng/mL respectively (Torrance and Cooper, 2010; Wikstrom et al., 2010). A study in rat model has shown that methylone is well incorporated in hair while cathinone and methcathinone are poorly incorporated (Kikura-Hanajiri et al., 2007).

4.7. Prevalence

Although the recreational use of synthetic cathinones is not new (e.g. methcathinone in the ex-Soviet Union in 1970s and 1980s and in the United States in 1990s), information about the currently prevalence of synthetic cathinones misuse in the population are very limited (namsdl, 2012). The emergence of six synthetic cathinones, all closely related to pyrovalerone, was reported in Germany between 1997 and 2004 (namsdl, 2012), but the use of Google Insights, an internet application used to track search terms, shows almost no searches for synthetic cathinones before 2008 (Google/insights, 2012). A significant increase of searches there was between 2009 and 2010 when the United Kingdom Poison Information Service received a number of inquiries regarding synthetic cathinones comparable to those for cocaine and MDMA (James et al., 2011; Google/insights, 2012; namsdl, 2012). A Finnish study which analyzed blood from suspected by police to drive under the effect of drugs found that 286 of 3000 specimens submitted for analysis contained 3,4-methylenedioxypyrovalerone (MDPV) (8.6%) (Kriikku et al., 2011). A Irish study which analyzed urine samples collected from patients receiving methadone maintenance found that 14% were positive to mephedrone and 3% were positive to methylone (McNamara et al., 2010). A self-report study on students of UK high school and college revealed that 20% had used mephedrone on at least one occasion, 4% reported daily use, and all daily users were under 21 years of age (Dargan et al., 2010). An online survey of club-goers in the UK found that 41% had used methedrone and 10% had used methylone. A third had used methedrone in the last month and 14% reported weekly assumption (Winstock et al., 2011). In an online survey conducted in late 2010 in collaboration with the UKs dance music magazine Maxmag, mephedrone was the fourth most-commonly used drug in the past year after cannabis, ecstasy and cocaine and it had been tried by 61% of respondents (EMCDDA, 2012). The American Association of Poison Control Centers reported 303 calls related to synthetic cathinones in 2010 and 6072 in 2011 (aapcc, 2012). Although limited, prevalence data currently available show a progressive increase in the spread of these substances justifying the concerns in the fields of drug policy, forensic toxicology and public health.

4.8. Patterns of use

The most common modality of consumption of synthetic cathinones are insufflation (snorting), or ingestion. Inhalation, sublingual and rectal administration and intramuscular or intravenous injection have also been described (Carhart-Harris et al., 2011; drugs-forum, 2012). Independently of the modalities of consumption, the psychoactive effects may be the same, but non-oral consumption could produce shorter duration of action (drugs-forum, 2012). Users information suggests that doses range is between 1 mg and 1 g of substance even if there are no data on purity of the products. Redosing in a single session is very common because some synthetic cathinones have a short duration of action (drugs-forum, 2012; bluelight, 2012; erowid, 2012). Users also reported the consumption of synthetic cathinones in combination or in association with other drugs in order to enhance the desired effects or reduce the harmful effects. In particular, the most reported combination are between synthetic cathinones and cocaine, amphetamines, methamphetamines, caffeine, hallucinogenes, kratom, other synthetic cathinones (to enhance stimulant and entactogen effects), alcohol and beta blocker (to counteract tachycardia), GBL, zopiclone (to produce visual hallucinations), pregabalin, famotidine, omeprazole, domperidone (to counteract stomach pain), opiates (speedball like-effects), cannabis, benzodiazepines (to counteract anxiety) (drugs-forum, 2012).

4.9. Medical use

As a result of their side effects, synthetic cathinones have received little consideration in the pharmacological therapy. Methcathinone was originally used as an antidepressant in the former Soviet Union in the 1930s, but very quickly it became a recreational drug (namsdl, 2012). Pyrovalerone and amfepramone have been used as anorectics, but they are currently obsolete. Bupropion is used as antidepressant and as an aid for those who wish to quit tobacco smoking (EMCDDA, 2012). Bupropion is a ring-substituted cathinones closely related to the synthetic cathinones found in legal highs. It acts as a dopamine and norepinephrine re-uptake inhibitor with stimulant-like effects in animals (Rau et al., 2005). Furthermore, it is an antagonist of neural acetylcholine nicotinic receptors (caymanchem/10488, 2012). Although at present there are no evidences supporting the hypothesis of a potential therapeutic role of bupropion in the treatment of synthetic cathinones induced dependence and craving, the structural and functional similarity between these molecules suggests a possible therapeutic role of bupropion in the treatment of addictive disorders related to the use of cathinone derivatives. Furthermore, some trials involving bupropion have demonstrated possible benefit in treating methamphetamine dependence in selected methamphetamine patients (Karila et al., 2010). In addition, a series of bupropion analogs were synthesized with the aim of developing medications for treating methamphetamine and cocaine dependence (Carroli et al., 2009) These data, considering the structural and functional similarity between synthetic catinones and methamphetamines, should stimulate new studies evaluating the effectiveness of bupropion in the treatment of synthetic cathinones induced dependence and craving.

5. Discussion

Since 2009, recreational products containing synthetic cathinones are on the rise. These substances, generally classified as research chemical, produce cocaine or amphetamine-like effects and they are used particularly by young people. The popularity of these substances may be due to various different reasons. First, although the products containing synthetic cathinones

are generally marketed as "not for human consumption", users utilize these substances because, like amphetamines or cocaine, they are able to produce strong stimulant effects. Second, these products are readily available in smart shops present on the internet and their price is affordable also by young people. 1 g of mephedrone costs approximately 18–35 euro and this quantity is sufficient for various doses (EMCDDA, 2012). Third, some molecules are still not controlled and this makes them enticing for people who want to use stimulants but are afraid of the legal consequences. Fourth, synthetic cathinones are not detected with commonly used screening tests but it is required the gas chromatography–mass spectrometry or liquid chromatography/mass spectrometry. This has important consequences, because it encourages cocaine or amphetamines users and curious people to use these substances and it makes difficult to verify abstinence from drugs of patients treated in rehabilitation centers. Fifth, commercial definitions such as "bath salts" and "plant fertilizer" can provide false assurances on the safety of these substances as drugs of abuse. Finally, the spread of synthetic cathinones may have been favored by the loss of purity of other stimulants such as cocaine or MDMA (Measham et al., 2010). The literature data and internet information have shown that these compounds may produce severe acute intoxication with high risk of fatal consequences related to the powerful stimulation of the catecholaminergic system (Meltzer et al., 2006; Durham, 2011). Furthermore, the dopaminergic stimulation of the reward system could explain the development of tolerance, abuse, dependence and withdrawal syndrome after frequent consumption of synthetic cathinones (Ross and Peselow, 2009). Thus, considering the data currently available about the toxicological effects of these substances, the alertness of scientific community is of great importance in order to monitoring and prevent the spread of synthetic cathinones.

6. Conclusion

Although synthetic cathinones are marketed as "bath salts" or "plants fertilizer", people utilize these compounds for their cocaine and amphetamine-like effects. The literature data and internet information clearly demonstrate the acute Cardiovascular and Central Nervous Systems toxicity of synthetic cathinones in combination with the high risk of death drug-related, abuse, tolerance and dependence. A common international action to ban the synthetic cathinones would be necessary to prevent the continual replacement of the molecules in the recreational products (Davies et al., 2010). In conclusion, the data currently available unequivocally show that the recreational use of synthetic cathinones must be considered highly dangerous to public health.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

Al-Halbori, M., 2005. The potential adverse effects of habitual use of *Catha edulis* (khat). Expert. Opin. Drug Saf. 4, 1145–1154.

Balint, E.E., Falkay, G., Balint, G.A., 2009. Khat—a controversial plant. Wien. Klin. Wochenschr. 121, 604–614.

Baron, D.N., 1999. A memorable experience: the qat party. BMJ 319, 500.

Borek, H.A., Holstege, C.P., 2012. Hyperthermia and multiorgan failure after abuse of bath salts containing 3,4-methylenedioxypyrovalerone. Ann. Emerg. Med., doi:10.1016/j.annemergmed.2012.01.005.

Brandt, S.D., Freeman, S., Summale, H.R., Measham, F., Cole, J., 2010. Analysis of NRG Legal highs in the UK: identification and formation of novel cathinones. Drug Test. Anal. 2, 377–382.

Brenneisen, R., Fisch, H.V., Koelbing, V., Geisshusler, S., Kalix, P., 1990. Amphetamine-like effect in humans of the khat alkaloid cathinone. Br. J. Clin. Pharmacol. 30, 825–828.

Carhart-Harris, R.L., King, L.A., Nutt, D.J., 2011. A web-based survey on mephedrone. Drug Alcohol Depend. 118, 19–22.

Carroli, F.I., Blough, B.E., Abraham, P., Mills, A.C., Holleman, J.A., Wolckenhauer, S.A., et al., 2009. Synthesis and biological evaluation of bupropion analogues as potential pharmacotherapies for cocaine addiction. J. Med. Chem. 52, 6768–6781.

Carter, N., Rutty, G.N., Milroy, C.M., Forrest, A.R., 2000. Deaths associated with MBDB misuse. Int. J. Legal Med. 113, 168–170.

Centers for Control and Prevention (CDC), 2011. Emergency visits after use of a drug sold as "bath salts"—Michigan, November 13, 2010–March 31, 2011. MMWR Morb. Mortal. Wkly. Rep. 60, 624–627.

Colzato, L.S., Ruiz, M.J., Van den Wildenberg, W.P.M., Hommel, B., 2011. Khat use is associated with impaired working memory and cognitive flexibility. PLoS One 6, e20602.

Coppola, M., Mondola, R., 2012. 3,4-Methylenedioxypyrovalerone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. Toxicol. Lett. 5, 12–15.

Cozzi, N.V., Sievert, M.K., Shulgin, A.T., Jaco 3rd., P., Ruoho, A.E., 1999. Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines. Eur. J. Pharmacol. 381, 63–69.

Dargan, P.I., Albert, S., Wood, D.M., 2010. Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. QJM 103, 875–879.

Dargan, P.I., Sedefov, R., Gallegos, A., Wood, D.M., 2011. The pharmacology and toxicology of the synthetic cathinone mephedrone (4-methylmethcathinone). Drug. Test. Anal. 3, 454–463.

Davies, S., Wood, D.M., Smith, G., Button, J., Ramsey, J., Archer, R., et al., 2010. Purchasing legal highs on the Internet—is there consistency in what you get? QJM 103, 489–493.

Durham, M., 2011. Ivory wave: the next mephedrone? Emerg. Med. J. 28, 1059–1060.

Foltin, R.W., Schuster, C.R., 1982. Behavioral tolerance and cross-tolerance to DL-cathinone and D-amphetamine in rats. J. Pharmacol. Exp. Ther. 222, 126–131.

Gibbons, S., Zloh, M., 2010. An analysis of legal high mephedrone. Bioorg. Med. Chem. Lett. 20, 4135–4139.

Griffiths, P., Gossop, M., Wickenden, S., Dunworth, J., Harris, K., Lloyd, C.A., 1997. A transcultural patterned drug use: qat (khat), in the UK. Br. J. Psychiatry 170, 281–284.

Gustavsson, D., Escher, C., 2009. Mephedrone—internet drug which seems to have come and stay. Fatal cases in Sweden have drawn attention to previously unknown substances. Lakartidningen 106, 2769–2777.

Gygi, M.P., Fleckenstein, A.E., Gibb, J.W., Hanson, G.R., 1996. Role of endogenous dopamine in the neurochemical deficits induced by methcathinone. J. Pharmacol. Exp. Ther. 283, 1350–1355.

Halbach, H., 1972. Medical aspects of the chewing of khat leaves. Bull. World Health Organ. 47, 21–29.

Hassan, N.A., Gunaid, A.A., Murray-Lyon, I.M., 2007. Khat (*Catha edulis*): health aspects of khat chewing. East Mediterr. Health J. 13, 706–718.

James, D., Adams, R.D., Spears, R., Cooper, G., Lupton, D.J., Thompson, J.P., et al., 2011. Clinical characteristics of mephedrone toxicity reported to the UK Poison Information Service. Emerg. Med. J. 28, 686–689.

Kalix, P., 1986. The releasing effect of the isomers of the alkaloid cathinone at central and peripheral catecholamine storage sites. Neuropharmacology 25, 499–501.

Kalix, P., 1990. Pharmacological properties of the stimulant khat. Pharmacol. Ther. 48, 397–416.

Kalix, P., 1992. Cathinone: a natural amphetamine. Pharmacol. Toxicol. 70, 77–86.

Kalix, P., 1996. Catha edulis, a plant that has amphetamine effects. Pharm. World Sci. 18, 69–73.

Karila, L., Reynaud, M., 2011. GHB and synthetic cathinones: clinical effects and potential consequences. Drug Test. Anal. 9, 552–559.

Karila, L., Weinstein, A., Aubin, H.J., Benyamina, A., Reynaud, M., Batki, S.L., 2010. Pharmacological approaches to methamphetamine dependence: a focused review. Br. J. Clin. Pharmacol. 69, 578–592.

Kelly, J.P., 2011. Cathinone derivatives: a review of their chemistry, pharmacology and toxicology. Drug Test. Anal. 3, 439–453.

Kikura-Hanajiri, R., Kawamura, M., Saisho, K., Kodama, Y., Goda, Y., 2007. The disposition into hair of new designer drugs: methylone, MBDB and methcathinone. J. Chromatogr. B: Analyt. Technol. Biomed. Life Sci. 855, 121–126.

Kriikku, P., Wilhelm, L., Schwarz, O., Rintatalo, J., 2011. New designer drug of abuse: 3,4-methylenedioxypyrovalerone (MDPV). Findings from apprehended drivers in Finland. Forensic Sci. Int. 210, 195–200.

Maskell, P.D., De Paoli, G., Seneviratne, C., Pounder, D.J., 2001. Mephedrone (4-methylmethcathinone)-related deaths. J. Anal. Toxicol. 35, 188–191.

McNamara, S., Stokes, S., Coleman, N., 2010. Head shop compound abuse amongst attendees of the Drug Treatment Centre Board. Intern. Med. J. 103, 134–137.

Measham, F., Moore, K., Newcombe, R., Welch, Z., 2010. Tweaking, bombing, dabbing and stockpiling: the emergence of mephedrone and the perverity of prohibition. Drug Alcohol Today 10, 14–21.

Meltzer, P.C., Butler, D., Deschamps, R., Madras, B.K., 2006. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. J. Med. Chem. 49, 1420–1432.

Meyer, M.R., Maurer, H.H., 2010. Metabolism of designer drugs of abuse: an updated review. Curr. Drug Metab. 11, 468–482.

Meyer, M.R., Wilhelm, J., Peters, J., Maurer, H.H., 2010. Beta-keto amphetamines: studies on the metabolism of the designer drug mephedrone, and toxicological detection of mephedrone, butylone, and methylone in urine using gas chromatography–mass spectrometry. Anal. Bioanal. Chem. 397, 1225–1233.

Mugele, J., Nanagas, K.A., Tormoehlen, L.M., 2012. Serotonin syndrome associated with MDPV use: a case report. Ann. Emerg. Med., http://dx.doi.org/10.1016/j.annemergmed.2011.11.033.
Murray, B.L., Murphy, C.M., Beuhler, M.C., 2012. Death following recreational use of designer drug Bath salts containing 3,4-Methylenedioxypyrovalerone (MDPV). J. Med. Toxicol., doi:10.1007/s13181-011-0196-9.
Nencini, P., Amiconi, G., Befani, O., Abdullahi, M.A., Anania, M.C., 1984. Possible involvement of amine oxidase inhibition in the sympathetic activation by khat (*Catha edulis*) chewing in humans. J. Ethnopharmacol. 11, 78–86.
Ojanpera, I.A., Heikman, P.K., Rasanen, I.J., 2011. Urine analysis of 3,4-methylenedioxypyrovalerone in opioid-dependent patients by gas chromatography–mass spectrometry. Ther. Drug Monit. 33, 257–263.
Panders, T.M., Gestring, R., 2011. Hallucinatory delirium following use of MDPV: bath salts. Gen. Hosp. Psychiatry 33, 525–526.
Prosser, J.M., Nelson, L.S., 2012. The toxicology of bath salts: a review of synthetic cathinones. J. Med. Toxicol. 8, 33–42.
Rau, K.S., Birdsall, E., Hanson, J.E., Johnson-Davis, K.L., Carrol, F.I., Wilkins, D.J., et al., 2005. Bupropion increases striatal vesicular monoamine transport. Neuropharmacology 49, 820–830.
Regan, L., Mitchelson, M., Macdonald, C., 2011. Mephedrone toxicity in Scottish emergency department. Emerg. Med. J. 28, 1055–1058.
Ross, S., Peselow, E., 2009. The neurobiology of addictive disorders. Clin. Neuropharmacol. 32, 269–276.
Schechter, M.D., 1990. Dopaminergic nature of acute cathine tolerance. Pharmacol. Biochem. Behav. 36, 817–820.
Schifano, F., Ricciardi, A., Corazza, O., Deluca, P., Davey, Z., Rafanelli, C., et al., 2010. New drugs of abuse on the web: the role of the Psychonaut Web Mapping Project. Riv. Psichiatr. 45, 88–93.
Schorno, X., Steinegger, E., 1979. CNS-active phenylpropylamines of *Chata edulis* Forsk (*Celastraceae*) of Kenyan origin. Experientia 35, 572–574.
Spiller, H.A., Ryan, M.L., Weston, R.G., Jansen, J., 2011. Clinical experience with and analytical confirmation of bath salts and legal highs(synthetic cathinones) in the United States. Clin. Toxicol. (Phila.) 49, 499–505.
Strano-Rossi, S., Cadwallader, A.B., de la Torre, X., Botrè, F., 2011. Toxicological determination and in vitro metabolism of the designer drug methylenedioxypyrovalerone (MDPV) by gas chromatography/mass-spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. Rapid Commun. Mass Spectrom. 24, 2706–2714.
Torrance, H., Cooper, G., 2010. The detection of mephedrone (4-methylmethcathinone) in 4 fatalities in Scotland. Forensic Sci. Int. 202, e62–e63.
Walsh, C., 2011. Drugs, the internet and change. J. Psychoactive Drugs 43, 55–63.
Wikstrom, M., Thelander, G., Nystrom, I., Kronstrand, R., 2010. Two fatal intoxications with the new designer drug methedrone (4-methoxymethcathinone). J. Anal. Toxicol. 34, 594–598.
Winstock, A.R., Mitcheson, L.R., Marsden, J., 2010. Mephedrone: still available and twice the price. Lancet 376, 1537.
Winstock, A.R., Mitcheson, L.R., Deluca, P., Davey, Z., Corazza, O., Schifano, F., 2011. Mephedrone, new kid for the chop? Addiction 106, 154–161.
Wood, D.M., Davies, S., Puchnarewicz, M., Button, J., Archer, R., Ovaska, H., et al., 2010. Recreational use of mephedrone (4-methylmethcathinone) with associated sympathomimetic toxicity. J. Med. Toxicol. 6, 327–330.
Yousef, G., Huq, Z., Lambert, T., 1995. Khat chewing as a cause of psychosis. Br. J. Hosp. Med. (Lond.) 54, 322–326.
Zaitus, K., Katagi, M., Kamata, H.T., Kamata, T., Shima, N., Miki, A., et al., 2009. Determination of the metabolites of the new designer drugs bk-MBDB and bk-MDEA in human urine. Forensic Sci. Int. 188, 131–139.

Further reading (Web references)

http://www.aapcc.org/dnn/portals/o/Bath%205alts%20Data%alta%20for%20Website%201.5.2012.pdf (visited January 16, 2012).
http://www.acep.org/Content.aspx?id=77160 (visited January 11, 2012).
http://www.bluelight.ru (visited January 16, 2012).
http://www.caymanchem.com/app/template/Product.vm/catalog/10624 (visited January 17, 2012).
http://www.caymanchem.com/app/template/Product.vm/catalog/10488 (visited March 09, 2012).
http://www.droganews.t/news/1091/Dipendenza%3A_modelli_ed_effetti_dannosi_html (visited January 11, 2012).
http://www.drugrecognitionexpert.us/2011/02/bath-salts-mdpv/ (visited January 12, 2012).
http://www.drugs-forum.com (visited January 12, 2012).
http://www.emcdda.europa.eu/publications/drug-profiles/synthetic-cathinones (visited January 11, 2012).
http://www.erowid.org (visited January 12, 2012).
http://www.google.com/insights/search/ (visited January 15, 2012).
http://www.justice.gov/ndic/pubs44/44571/44571p.pdf (visited January 11, 2012).
http://www.justice.gov/dea/programs/forensicsci/microgram/journal_v5_num14/pg1.html (visited January 11, 2012).
http://www.namsdl.org/documents/ACMDCathinonesReport.pdf (visited January 18, 2012).
http://www.scribd.com/doc/57078733/Bath-Salt (visited January 11, 2012).