The Laboratory Medicine at the University Hospital Basel provides the following services to the hospital and many external customers:

- > 4.0 Mio. results in 2015
- > 500 different analytes in plasma, serum, blood, urine, faeces, meconium, saliva
- Working hours: 365 days/year, 24 hours/day
- Very fast *turn-around* times for a selected panel of analytes
- Special diagnostics fields of toxicology, drug monitoring, protein and cerebrospinal fluid analytics.

The analytical techniques used comprise immunological, chemical and enzymatic methods as well as electrophoresis, LC-MS and GC-MS. Most of the analyses are performed with highly automated instruments; the chromatographic instruments are all equipped with autosamplers.

**Case:**

At 1:00 a.m. a 23 year old male patient is admitted to the emergency department of the University Hospital in Basel. He was very agitated, had a combative violent behaviour and hallucination. He has been found in his home standing on his bed complaining of mice everywhere. He was given the antidote for opiate intoxications without any effect.

The classical drugs of abuse screening tests in the laboratory were negative. The physicians then suspected the intake of legal highs or research chemicals and sent a urine and a blood sample to the laboratory.
Questions:
1. Which compounds are used as legal highs or research chemicals?
2. What is the action of these substances?
3. Which is/are the method(s) of choice for the analysis of these compounds? Which are the advantages or the disadvantages of the different methods?
4. How is the legal situation with these compounds in Switzerland?

Literature:
1. Clinical Toxicology 2011;49:499-505
2. Clinical Toxicology 2012;50:15-24
3. The American Journal of Drug and Alcohol Abuse 2012;38:176-180
“Bath Salt” Ingestion Leading to Severe Intoxication Delirium: Two Cases and a Brief Review of the Emergence of Mephedrone Use

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Background: Recreational use of designer substances containing synthetic cathinones such as mephedrone, commonly sold as “bath salts,” has recently been increasing in the United States (National Institute on Drug Abuse. Available at: http://www.nida.nih.gov/about/welcome/MessageBathSalts211.html. Accessed March 25, 2011; The Washington Post. Available at: http://www.washingtonpost.com/national/officials-fear-bath-salts-becoming-the-next-big-drug-menace/2011/01/22/ABybyRJ_story.html. Accessed March 25, 2011). “Bath salt” ingestion can generate an intense stimulant toxidrome and has been associated with significant morbidity. Objectives: The authors seek to alert clinicians to the potential for profound delirium, psychosis, and other medical and behavioral sequelae of “bath salt” use. Methods: Case series. Results: We describe our recent experience with two highly agitated and delirious patients following “bath salt” ingestion and offer a brief review of the emergence of this phenomenon. Conclusions: Challenges and strategies surrounding diagnosis and treatment are described, which may be useful as “bath salt” use becomes more widespread. Scientific Significance: As an emerging trend, bath salt intoxication delirium appears to cause intense psychosis that can be managed with antipsychotic medications. Clinicians should be aware of this phenomenon until more precise detection methods are available.

Keywords: bath salts, mephedrone, delirium

INTRODUCTION

Since late 2010, news media outlets in the United States have reported a recent surge in the sale, consumption, and abuse of synthetic stimulants packaged and sold as “bath salts,” which have been found to contain the stimulant compound mephedrone (4-methylmethcathinone; Table 1) (1,2). Mephedrone is among several synthetic derivatives of cathinone, a schedule I stimulant substance found in the khat (Catha edulis) plant grown in east Africa. These synthetic stimulant compounds have been previously reported in the United Kingdom and elsewhere in Europe to produce a profound deliriogenic toxidrome, generating intense agitation and hallucinations. Similar to other abusable stimulant agents (cocaine, amphetamines, methylenedioxymethamphetamine (MDMA)), patients who have ingested the stimulants found in “bath salts” have had severe, protracted toxidromes that require general hospital admission for adequate management of sustained physical and behavioral sequelae. Although US law enforcement has verified the presence of mephedrone and other synthetic cathinone derivatives found in “bath salts,” we are unaware of any published confirmed patient cases outside of Europe, possibly due to hospital toxicology labs not yet routinely testing for the presence of these compounds. We anticipate that clinicians will increasingly encounter similar delirious toxidromes as the use becomes more prevalent. Maintaining awareness of this phenomenon when evaluating patients with toxic ingestions will be helpful until confirmatory testing becomes more widely available in clinical settings. We report our recent experiences with two patients seen in psychiatric consultation on a general hospital medical unit following the purposeful ingestion of “bath salts.”

CASE 1

“Mr. A,” a 38-year-old Caucasian male without prior history of psychosis, was taken to an outside hospital by Emergency Medical Services (EMS) after his significant other called to report that Mr. A was seeing snakes and acting strangely. The patient was found in his home standing on his bed complaining of “snakes everywhere.”
He was given 2 mg of naloxone twice at the scene with no improvement. After 45 minutes of verbal de-escalation by medics, the patient was restrained to the EMS cot and taken to an outside hospital.

While in the outside hospital emergency department (ED), he was tachycardic (EKG revealed heart rate of 144, occasional premature ventricular contractions (PVCs), and QTc of 430 ms) and his temperature was 100.8°F; he was restrained but refused to be covered with a blanket due to fears that “scorpions” would bite him. The patient’s significant other provided further history that Mr. A had ingested “bath salts” packaged under the name “Arctic Blast,” twice over the prior 2 days. The ED physician documented that police found “bath salts” in the patient’s personal effects. In the triage area, Mr. A was complaining of “things crawling on him and in his hair.” He remained agitated in the ED and received 3 mg of IV lorazepam over the course of 4 hours with 2 L of IV fluids. Laboratory assessment revealed elevated hemoglobin and hematocrit, consistent with his history of polycythemia. His white blood cell count and platelets were normal. He also had negative acetaminophen and salicylate levels, glucose of 99, and TSH within normal limits. Chemistry panel and liver function tests were unremarkable. His mental state examination (MMSE) was 28/30 (missed the floor of the hospital, one serial 7). His significant other was contacted who agreed with the history he presented.

Over the next 24 hours, Mr. A showed sustained improvements in attention, awareness, focus, concentration, and speed of thought. He had no residual psychotic symptoms and performed normally on further bedside cognitive screening. He was discharged the following day with his significant other. He described his ingestion as one of the worst experiences of his life and was adamant that he would not engage in a repeat ingestion.

### TABLE 1. Various reported “bath salt” trade names (1,2).

<table>
<thead>
<tr>
<th>Bath salt trade names</th>
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<tbody>
<tr>
<td>Ivory Wave</td>
</tr>
<tr>
<td>Purple Wave</td>
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<tr>
<td>Red Dove</td>
</tr>
<tr>
<td>Blue Silk</td>
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<tr>
<td>Bloom</td>
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<tr>
<td>Cloud Nine</td>
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<tr>
<td>Ocean Snow</td>
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<tr>
<td>Lunar Wave</td>
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<tr>
<td>Vanilla Sky</td>
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<tr>
<td>White Lightning</td>
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<tr>
<td>Scarface</td>
</tr>
<tr>
<td>Hurricane Charlie</td>
</tr>
<tr>
<td>Posh</td>
</tr>
<tr>
<td>Arctic Blast</td>
</tr>
</tbody>
</table>

Mr. B, a 26-year-old Caucasian male, presented to the ED 2 days after nasally insufflating “four lines” of “bath salts” (later approximated to be 2 g of “Posh Aromatherapy Bath Salts” in an 8-hour period) that he purchased at a local gas station. He reported first consuming “bath salts” 1 month prior to admission and had been snorting smaller amounts on a daily basis since that time. Mr. B reported auditory hallucinations, as well as prominent illusions and feelings of detachment and derealization following his daily use. He reported developing tolerance to his daily use of smaller amounts (between 0.25 and 0.5 g) and decided to use a larger amount prior to being admitted to the hospital.

In addition to its usual effects, following his 2 g insufflation, Mr. B developed prominent paranoia, suicidal ideation, confusion, delirium, tremors, hyperreflexia, myoclonus, and amnestic effects. He had significant difficulty remembering details of his behavior in the 2 days that elapsed since his overdose, although we verified later that he was briefly in the custody of law enforcement, having been found after driving his car into a ditch. He recalled the desire to die at that time, vaguely recalling the desire to jump in front of a car while standing along a freeway. He described intense auditory hallucinations and paranoid delusions of being followed by “unmarked...
cups” and was picking in the air at apparent visual hallucinations. His chemistries at admission included slightly elevated creatinine (1.33), mildly elevated transaminases (ALT 64, AST 50), and CK of 1665. He was afebrile, but had mild hypertension and tachycardia, although his EKG was otherwise unremarkable. His comprehensive urine toxicology screen was negative for any identifiable substances. His roommate also later confirmed that Mr. B had only ingested “bath salts” and no other substances.

While hospitalized, Mr. B continued to remain restless, paranoid, and at times agitated and inattentive. He had limited awareness of his surroundings and continued to hallucinate up through 48 hours post-ingestion. He began to gradually improve with IV fluids and a total of 5 mg of IV lorazepam. Additionally, we administered two oral doses of risperidone 0.5 mg, which he tolerated without any adverse effects and correlated with a rapid improvement in his symptoms over the subsequent 24 hours. By 96 hours post-ingestion, his chemistries, liver function tests, CK, and vital signs all normalized. His delirium resolved, and his thinking was organized, aware, and goal directed, with an MMSE of 29/30 (missing one recall item). His neuromuscular exam was normal. His fluids, lorazepam, and risperidone were discontinued, and he was discharged home.

DISCUSSION

Our cases represent the emerging awareness of the potential for a severe, toxic delirium generated by “bath salts,” which are becoming more widely used and consumed for recreational intoxication in the United States. Alerts from the National Institute on Drug Abuse suggest that this trend is increasing, reporting that calls to poison control centers reporting cases of “bath salt” intoxication in the first 2 months of 2011 exceeded the total number of calls for this reason received for the entirety of 2010 (1). Sold in gas stations, convenience stores, over the Internet, and drug paraphernalia “head shops,” numerous states have enacted legislation to classify mephedrone and similar synthetic cathinone-derivative compounds as controlled substances (2). The United States Drug Enforcement Administration has reported that mephedrone is present in products promoted as “bath salts,” as well as in other substances sold on the Internet as “research chemicals” or “plant food” (3). Similar to “bath salts,” mephedrone and other mixed synthetic cathinone derivatives have been detected in samples purchased and analyzed in the United Kingdom sold as “plant food” and “NRG-1” (4,5). Mephedrone has been detected in similar substances seized by European law enforcement with increasing frequency since 2008, culminating its designation as a controlled substance in the United Kingdom in April 2010 (6,7). The rapid growth of the popularity of mephedrone and other cathinone-derivative stimulants sold as “bath salts” in a short period of time has been partially attributed to aggressive Internet marketing as well as social networking sites serving as a forum to spread interest among young adults (8).

Although the synthesis of mephedrone was first described in 1929, there is a limited amount of published data surrounding its bioactive properties (9). Mephedrone, one of the numerous beta-keto analogues of amphetamine, shares psychoactive properties similar to cocaine, amphetamines, and MDMA (10). As cathinones bind to noradrenaline, dopamine, and serotonin transporters, mephedrone is expected to act as a stimulant by promoting the release of monoamine neurotransmitters and likely inhibiting their reuptake (9). Experiences with patients who have ingested similar white powdery substances, confirmed to contain mephedrone, have been reported in the United Kingdom. The most common clinical findings in these cases were tachycardia, hypertension, and agitation, similar to the sympathomimetic toxidromes observed following MDMA or cocaine use (11). Mydriasis, anxiety, agitation, paranoia, bruxism, aggression, depression, hallucinations, delusions, and manic behavior and seizures have also been reported from mephedrone use (9,12,13).

Serious complications of mephedrone ingestion have been reported in the UK hospitals, including serotonin syndrome, delirium due to mephedrone-induced hyponatremia, as well as acute myocarditis (14–16). Forensic examiners in the Netherlands recently attributed the death of a 36-year-old man to mephedrone ingestion, following a period of excited, agitated delirium (17).

Limited data exist regarding the most effective treatments for mephedrone toxidromes. However, as in the management of other sympathomimetic toxidromes, a case series published in the United Kingdom supports the use of benzodiazepines for treating the agitation associated with the acute toxidrome (11). Based on these previously published reports in Europe, poison control protocols, and concerns for exacerbation of hyperthermia, rigidity, or seizures with antipsychotic use, a mixture of benzodiazepines, intravenous fluids, and other supportive measures was initiated following arrival to the ED. Being unaware of other confirmed cases of “bath salt” or mephedrone toxicity reporting the use of antipsychotics for the treatment of post-ingestion delirium, our patients were closely monitored on the general medical floor ( telemetry, seizure precautions, constant observation) once antipsychotics were initiated for the protracted delirious symptoms that did not show sustained response to initial treatment. The use of intramuscular haloperidol and oral risperidone in our patients did not lead to any observable adverse effects and correlated with a rapid reduction of their residual agitation and delirious features.

Among the potential diagnostic challenges for clinicians in the diagnosis of “bath salt” intoxication delirium is the lack of routine toxicology screening for mephedrone and other synthetic cathinones. Assays for these compounds for clinicians seeking same-day results have not yet been developed for widespread routine hospital use in the United States (Michael Bissell, personal communication, August 3, 2011). To our knowledge, only one facility nationally provides access to “send-out” testing, which may not be immediately useful.
for practicing clinicians (18). Novel methods developed to detect mephedrone in urine have only been recently described (19). Furthermore, we also encountered each of our patients more than 18 hours following their “bath salt” ingestions. This could complicate further post-metabolism detection efforts, as the human toxicokinetics of mephedrone have not been clearly established (19).

However, as government law enforcement bulletins report that “bath salts” found in the United States contain mephedrone and other synthetic cathinones, we believe that a synthetic cathinone ingestion remains highly likely via the “bath salts” consumed by our patients given the history, corroboration of collateral informants, and clinical similarity to cases confirmed by serum toxicology in Europe (11,17). Despite Mr. A’s initial presumptive positive result for PCP at the outside hospital, this was unable to be verified through further confirmatory testing. If his protracted symptoms were solely caused by a substantive PCP ingestion, a confirmable presence on toxicology screening would seem more likely. His clinical presentation also lacked other acute features of PCP intoxication such as nystagmus, intolerance to pain, and ataxia. Although contamination with intoxicants other than synthetic cathinones could be possible among the variety of “bath salts” available for purchase, such impurities have not been described in laboratory analysis of European samples (4,5). The possibility of mephedrone causing false-positive PCP result also cannot be excluded, as mephedrone or other synthetic cathinones were not among the 30 potential cross-reactive substances tested by the manufacturer in the outside hospital’s PCP assay (20). We are unaware of other published reports in Europe raising this question, although our laboratory toxicology director has described several other similar recent, unexpected cases of initial presumptive positive PCP screens that were not reproducible through further confirmatory testing, suggesting that this possible phenomenon warrants further research (Michael Bissell, personal communication, August 3, 2011). We suspect that fellow clinicians may encounter similar negative drug screens or possible other confounding data until specific tests for mephedrone or other synthetic cathinones are developed for routine use.

As the use of “bath salts” continues to surge, clinicians should be aware of this emerging trend as an explanation for patients presenting with unexplained delirious toxicidromes or secondary psychoses, especially if routine toxicology screens may not detect the presence of these agents. Following a literature search, we remain unaware of other confirmed cases published in scientific journals of patients presenting in the United States with mephedrone intoxication; however, being mindful of the possible presence of synthetic cathinones in “bath salt” ingestions would be reasonable until broader detection of these compounds is routinely available. Beyond the supportive management necessary for common recreational drug toxicidromes, clinicians should remain vigilant for the risk of increasing morbidity and mortality from protracted agitated delirium, as well as the possibility of more ominous neurologic and cardiac sequelae derived from “bath salt” ingestion.

**Declaration of Interest**
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

**REFERENCES**


‘Legal Highs’ – novel and emerging psychoactive drugs: a chemical overview for the toxicologist

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Introduction. ‘Legal highs’ are psychoactive chemicals which are sold from ‘head shops’, the internet and from street suppliers and may be possessed without legal restriction. An increase in the marketing of these materials has resulted in a corresponding increase in published reports of their adverse effects. However, a lack of primary literature pertaining to their chemistry, pharmacology and toxicology, makes an evaluation of their harm difficult. This review covers the basic chemistry of these novel psychoactive compounds and relates them to endogenous neurotransmitters and existing drugs of abuse.

Methods. A survey of the internet was used to identify websites that are marketing ‘legal highs’ in the UK. Trivial and systematic chemical compound names, for example methoxetamine, 4-methoxyphencycline, 4-fluorotropacocaine and ethyl phenidate were entered into PubMed to retrieve data on these compounds. This search elicited no citations. Other search terms which were more fruitful included desoxypipradrol, diphenylprolinol, methylenedioxy-2-amino-indane and methylenedioxy-2-amino-tetralin, alpha-methyltryptamine and 5-methoxy-\(\text{N},\text{N}^*\)-diallyl-tryptamine.

Results. ‘Legal highs’ from the phenylethylamine, cocaine, tryptamine and phencyclidine classes are increasingly being marketed and, in the majority of cases, little is cited in the literature on their true chemical identity, pharmacology or toxicology.

Conclusions. ‘Legal highs’ are gaining in popularity and present clear challenges to toxicologists and society as a whole. Whilst improved use of existing legislation and development of new legislation can be used to reduce the supply of these materials, investment in better education for young people on the harms associated with ‘legal highs’ is needed.

Keywords Amphetamines; Cathinones; Cocaine; Herbal highs; Mephedrone; Neurotransmitters; PCP; Phenylethylamines; Tryptamines
This review will describe the various sources of psychoactive compounds in nature and show that many of the 'legal highs' currently emerging (and our existing controlled drugs of abuse) have a high degree of structural similarity with endogenous neurotransmitters. Examples of naturally occurring phenylethylamines and their synthetic derivatives will be described and compounds that are related to the natural product cocaine and the dissociative anaesthetics ketamine and phencyclidine will also be highlighted. Some of the new synthetic tryptamine analogues will also be mentioned and their structural similarity to serotonin and the older psyche-delic drugs such as LSD-25 will be demonstrated.

Methods
A survey of the internet was used to identify websites that are marketing 'legal highs' in the United Kingdom. Trivial and systematic chemical compound names such as methoxetamine, 4-methoxy-phencyclidine and 3-methoxy-phencycline were also entered into PubMed in an attempt to retrieve data on these compounds. This search elicited no citations. Other search terms which were more fruitful included desoxyxipipradrol, diphenylprolinol, methylenedioxy-2-amino-indane and methylenedioxy-2-amino-tetralin, alpha-methyltryptamine and 5-methoxy-N,N-diallyl-tryptamine.

Structural similarity of many 'legal highs' and endogenous neurotransmitters
Many of the synthetic and natural psychoactive substances not only bind to receptors and exert their effects, but also are analogues of endogenous neurotransmitters and have the ability to bind to the dedicated transport systems for these

![Fig. 1. Structures of natural product psychoactive compounds.](image1)

![Fig. 2. Natural and synthetic GABA-mimetics.](image2)

![Fig. 3. Psilocybe psychoactive alkaloids have similarity to serotonin.](image3)
neurotransmitters and inhibit their reuptake. The similarity that exists between the psychoactive substance phenylethylamine, amphetamine (amfetamine) and tryptamine and dopamine, norepinephrine (noradrenaline) and serotonin can be seen readily (Fig. 5). The simple structural motif of phenylethylamine exists in dopamine and norepinephrine, as it does in amphetamine (α-methyl phenylethylamine). The methyl group of amphetamine is in the alpha position next to the nitrogen atom. One can also see how similar tryptamine is to serotonin, differing only in the absence of a hydroxyl group on the aromatic ring. These similarities undoubtedly contribute to the ability of phenylethylamine, amphetamine and tryptamine-related compounds to elicit psychoactivity.

Further examples include the hallucinogen, mescaline, from the psychoactive cactus Peyote\textsuperscript{17} (\textit{Lophophora williamsii}) and cathinone from Khat (\textit{Catha edulis}).\textsuperscript{18} Peyote is widely available in the United Kingdom as a house plant and Khat is flown in daily from East Africa, and the leaves are chewed by members of the Somali and Yemeni communities in the United Kingdom in a social setting.\textsuperscript{19} Both of these psychoactive natural products have the structural motif that resembles phenylethylamine, amphetamine and tryptamine-related compounds to elicit psychoactivity.

Common horticultural plants and trees, particularly those of the pea family (Fabaceae) also contain psychoactive phenylethylamines such as hordenine\textsuperscript{20} and surprisingly even food plants such as the peel of bitter orange (\textit{Citrus aurantium}) have small amounts of compounds such as synephrine,\textsuperscript{21} a phenylethylamine related to ephedrine (Fig. 6). Weight-loss preparations are being marketed globally through the internet and contain extracts of bitter orange peel, presumably because of the stimulant properties of synephrine, but there are the same risks of tachycardia, hypertension and palpitations associated with this compound as there are with phenylethylamines in general.\textsuperscript{22}

**Mephedrone and the cathinones**

In 2009 there was an ‘explosion’ in the marketing of mephedrone\textsuperscript{23} and very similar compounds broadly termed cathinones due to their similarity to cathinone itself (Fig. 7). Mephedrone is the $4'$-methyl-$N$-methyl analogue of cathinone and was marketed as Miaow-Miaow and MCAT and sold through many internet websites as ‘plant food’, ‘pond cleaner’ and even ‘bath salts’. This compound has clear similarity to the amphetamines, but having a ketone group beta to the nitrogen atom and directly next to the aromatic ring (Fig. 7). Other cathinone analogues that were appearing at the same time included methyline,\textsuperscript{24} which is similar to Ecstasy.

\[\text{Epibatidine, an analgesic pyridine alkaloid from Epipedobatides tricolor.}\]

\[\text{Fig. 4.}\]

\[\text{Many drugs of abuse share structural similarity with our endogenous neurotransmitters.}\]

\[\text{Fig. 5.}\]

\[\text{Fig. 6.}\]
(methylenedioxy-methylamphetamine; MDMA), having only a carbonyl group in place of a methylene moiety. As these compounds are similar chemically to MDMA and methamphetamine, the concern was that they might not only exhibit the same psychoactivity but also the same neurotoxicity as these compounds. Mephedrone was either insufflated or taken orally in capsules, whereas users of methylone preferred the oral route due to the high nasal irritancy of this compound. Users reported stimulation and cocaine-like effects and mephedrone was (and still is) highly popular.25 Recent data has shown that mephedrone increases dopamine and serotonin concentrations in the nucleus accumbens of rats.26

The widespread appearance of mephedrone and related compounds was also possibly due to the ease of synthesis of this compound (Fig. 8). Starting with the solvent toluene, Friedel–Crafts acylation with propanoyl chloride in the presence of aluminium chloride as a catalyst, yielded a mixture of isomers but predominantly the para isomer due to steric hindrance at the ortho position. Simple addition of bromine in a solvent to the product would yield the alpha-bromo adduct which with the addition of an excess of methylamine would yield mephedrone in high yield and purity. The beauty of this synthesis is that the volatile methylamine can be removed very easily and the steps provide high purity and yield. Coupled with the ability to start with many different aromatic substrates, acylating groups (butanoyl, pentanoyl, hexanoyl) and even the final amines (ethylamine, pyrrolidine, piperidine), hundreds of cathinone analogues could potentially be produced.

The ease of production of many analogues was cause for concern and, coupled with the similarity of these compounds with existing phenylethylamines, the cathinones

Fig. 7. Natural and synthetic cathinones show striking similarity with amphetamines.

Fig. 8. Synthesis of mephedrone.

Fig. 9. A sample of mephedrone purchased from the internet (See colour version of this figure online).
were controlled by the UK Misuse of Drugs Act in April 2010. Before the ban, we acquired samples of mephedrone (Fig. 9) that were labelled specifically ‘not for human consumption’ but had the structure (correctly drawn). Anyone with a rudimentary chemical knowledge would realise how similar and close this compound is to the existing and controlled amphetamines. Our analysis showed that this material was of high-purity and, in this particular case, the hydrochloride salt (Fig. 10).

Following the control of these cathinones, another analogue appeared which was outside of the generic classification and possessed a naphthylene ring system rather than a benzene ring (Fig. 11). This compound, naphthylpyrovalerone (naphyrone; NRG-1), is related to the previously used fatigue medicine pyrovalerone. However, naphthylpyrovalerone is a highly potent triple reuptake inhibitor of nanomolar potency releasing dopamine, norepinephrine and serotonin at very low concentrations. Websites were offering to sell kilograms of this material packaged up in bags ready for distribution and given that an effective dose was as low as a few milligrams, the ability to titrate this low dose could have led to many cases of poisoning. Naphyrone was finally controlled by an amendment of the classification in July 2010, but it is possible that users avoided naphyrone due to concerns over its potency which was discussed on various internet drugs fora, and thankfully this material was never as popular as mephedrone was and is currently.

**New synthetic phenylethylamines**

Other ‘legal highs’ of the phenylethylamine class have also appeared on the internet and notably these are of the indane and tetralin groups (Fig. 12). Some of these compounds, such as methylenedioxy-2-amino-indane (MDAI), are selective serotonin releasers and are said to be ‘entactogens’ or ‘empathogens’, which are terms used to show that a compound causes social cohesion and empathy amongst users. This drug lacks the neurotoxicity seen with MDMA and is being marketed as a substitute for MDMA and the cathinone methylone.

Related compounds include the 5-iodo derivative being sold as NRG-2 and methoxyl-methyl-2-amino-indane (MMAI) (Fig. 12). Amino-tetralin stimulants have an additional methylene group making a six-membered ring rather than the five-membered ring seen in the amino-indanes. These include methylenedioxy-2-amino-tetralin (MDAT) and methylenedioxy-2-methylamino-tetralin (MDMAT). Both the indane and tetralin classes are still phenylethylamines but are in effect, ‘masked amphetamines’. MDAT and MDMA are commonly available and like the indanes are seen as substitutes for MDMA, though are purported to lack serotonin neurotoxicity. It should be noted, however, that whilst these early data suggest a lack of neurotoxicity of both these groups of compound, an in-depth evaluation of the general toxicity has yet to be conducted.

**Fig. 10.** $^1$H NMR spectrum of mephedrone (See colour version of this figure online).
Other cyclic derivatives are typified by diphenylprolinol (D2PM) and diphenylmethyl-pyrrolidine, which possess a five-membered pyrrolidine ring system and are dopamine and norepinephrine reuptake inhibitors. Diphenylprolinol is used as a catalyst in organic synthesis (Fig. 13). Six-membered analogues include pipradrol, a previously licensed medicine used for obesity, that is no longer used widely due to its potential for abuse. Pipradrol is classified under the UK Misuse of Drugs Act as a Class C substance being a dopamine and norepinephrine reuptake inhibitor.

The desoxy form, desoxypipradrol (Fig. 13), was developed by Ciba Geigy in the 1950s as a preparation to wake patients from anaesthesia and hence its German name ‘Weckamine’. Several reports of patients presenting in a highly agitated state with hallucinations, paranoia and classical amphetamine-like overdose symptoms, such as ‘formication’, after consuming ‘Ivory Wave’, which was later shown to contain desoxypipradrol, have been published. The long half-life of this compound, coupled with its low dose, show that it has significant potential toxicity, and the Advisory Council on Misuse of Drugs advised that an Open General Important Licence (OGIL) for this material be revoked at the end of 2010. Both of these classes of compound are structurally related to methylphenidate (Ritalin; Fig. 13). Other methylphenidate derivatives include the ethyl analogue currently marketed as ‘nopaine’ (ethylphenidate). In the body, this compound can be formed by ingestion of methylphenidate and ethanol, presumably by trans-esterification. It is a dopamine and norepinephrine reuptake inhibitor.

Cocaine derivatives

Synthetic derivatives of cocaine also have their representatives on the ‘legal high’ scene. These include the anaesthetic dimethocaine (larocaine) (Fig. 14), which has been shown to substitute for cocaine in trained rats, and 4-fluorotropacocaine. To date there are no published data on 4-fluorotropacocaine, whereas dimethocaine is a mild dopamine releasing agent compared to cocaine. Both of these compounds show structural similarity in terms of the number of bonds between the ester group and the nitrogen atom and 4-fluorotropacocaine possesses a tropane ring system like cocaine.
Ketamine and phencyclidine derivatives

Other marketed ‘legal highs’ include derivatives of the dissociative anaesthetics ketamine\(^9\) and phencyclidine.\(^{50}\) These compounds are antagonists of the NMDA receptor and are members of the phenyl cyclohexylamine class. Ketamine is used as a veterinary anaesthetic and in the military where rapid anaesthesia is required. Ketamine use is on the increase, particularly in Hong Kong, where it is currently the drug of choice, despite the risks of urinary and bladder dysfunction inherent in its use.\(^{51}\) A close analogue, methoxetamine (Fig. 15), has different substitution of the phenyl ring and amine functionality compared to ketamine. Very little is known about the chemistry, pharmacology and toxicology of this material. Given the close structural similarity of this compound with ketamine, it is highly likely that similar effects would be seen in humans.

Phencyclidine (PCP; Phenyl-Cyclohexyl-Piperidine), also known as ‘Angel Dust’ is controlled globally and is Class A in the United Kingdom. Analogues of phencyclidine are appearing, notably the 3- and 4-methoxy derivatives, which possess an additional methoxy group on the phenyl ring (Fig. 15). As with methoxetamine, there is a dearth of data on these close structural analogues of phencyclidine. We conducted one test purchase of the 4-methoxy analogue, which was a pure sample and of the correct chemical identity.

Synthetic and natural tryptamines

The ‘legal high’ scene is also seeing examples of tryptamine-derived drugs of abuse. Tryptamine (Fig. 16) bears close structural similarity with serotonin as do a number of ‘classical’ controlled drugs of abuse including psilocin, the alcoholic hydrolysis product of psilocybin from the ‘magic mushrooms’ of the genus Psilocybe and other closely related genera. Other examples include bufotenin, (a positional isomer of psilocin), which occurs in the skins of various species of toad of the genus Bufo.\(^{52}\)

Tryptamines in general have a history of being associated with the psychedelic movement, and these compounds are hallucinogenic and inhibit the reuptake and increase the release of serotonin. Other examples include more complex chemicals such as the well known LSD-25, with very strong effects on awareness and perception of the environment when doses of 20 μg are used. Two synthetic tryptamines related to these compounds are alpha-methyltryptamine (α-MT, AMT) and 5-methoxy-N,N-diallyl-tryptamine (5-MeO-DALT) (Fig. 16). There is more primary literature on these materials which release serotonin and dopamine and have structural similarity to serotonin which partially explains their effects.\(^{53,54}\) We conducted a test purchase of...
both materials, and structure elucidation has shown that they were of high-purity and correct identity. Compounds of this class can greatly alter perception, and this is highlighted by the tragic case of a 26-year-old man, who was killed after walking on to a motorway in Cambridgeshire in 2010. The Coroner recorded a ‘narrative verdict of death from injuries sustained when he was in collision with a lorry while under the influence of 5-MeO-DALT’ (http://www.cambridge-news.co.uk/Home/Familys-vow-over-legal-high-drugs-danger.htm).

Many analogues of tryptamine can be made by substitution on the nitrogen atom or the aromatic ring, and the chemistry to reach these compounds is relatively simple, unfortunately giving ease of access to many potential ‘legal highs’. There has also been an increase in the marketing of plant extract that contain psychoactive compounds of the tryptamine class. These include leaf material itself or extracts of the SE Asian tree, Mitragyna speciosa, which is sold in various concentrated strengths according to the extraction method used. This material is known as Kratom in Thailand or Biak-Biak in Malaysia and is a controlled substance in both countries. In Europe, samples bought from the internet can arrive as ‘buttons’ of dried extract, which is ingested orally and made up as a tea which has a bitter taste. Extracts have been confirmed to contain the alkaloid, mitragynine (Fig. 17) and its analogues, and this compound is a mu-opioid receptor agonist, which was investigated for its potential as a psychoactive compound. This material is known as Kratom in Thailand or Biak-Biak in Malaysia and is a controlled substance in both countries. In Europe, samples bought from the internet can arrive as ‘buttons’ of dried extract, which is ingested orally and made up as a tea which has a bitter taste. Extracts have been confirmed to contain the alkaloid, mitragynine, and its analogues, and this compound is a mu-opioid receptor agonist, which was investigated for its potential as a psychoactive compound.

Obviously, the strength of × 20 is unimportant for incense but would give users the false impression of the concentration of the material in the packaging for ingestion. This is fraught with danger, as little is known on the effects of Kratom resin and only full analytical chemistry would give rise to the concentration of psychoactive compounds present or even the presence of adulterant psychoactives. This highlights the problems associated with herbal and natural product ‘legal highs’ in general as their chemical analysis is highly complex, and there is, of course, the possibility that suppliers could add other psychoactive compounds to these materials which can cause even further problems in terms of polypharmacology and toxicology.

Seeds from members of the morning glory family, Convolvulaceae, have a long history of usage as psychoactive materials. The seeds from species of this family include Hawaiian Baby Woodrose (Argyreia nervosa), Ipomoea sp. and Convolvulus sp which are marketed through the internet as ‘ethnobotanicals’ to enhance memory. These seeds contain alkaloids of the ergot type such as ergine (Fig. 18), also known as lysergamide or lysergic acid amide, which has a close chemical structure to LSD-25, but lacking just two ethyl groups on the nitrogen atom. A whole range of these natural products are present in the seeds from this family, and their ability to cause psychosis are demonstrated by two cases of human consumption of the seeds of Hawaiian Baby Woodrose resulting in one fatality from jumping from a building; ergine was present in the blood and urine of this individual.

It is the ability of these ‘reality-distorting’ materials to cause such accidents that makes these materials potential dangerous as ‘legal highs’. They are, however, not as popular as stimulants such as the now controlled mephedrone, and it is possible that the majority of ‘legal high’ users avoid them because of the possibility of accidents following ingestion.

Salvia divinorum

As with Kratom, herbal material and extracts of the psychedelic sage (Salvia divinorum, Lamiaceae), which is a member of the mint family, can be readily purchased through the internet and is still legal in many countries, including the United Kingdom. Live plants and leaf cuttings can be obtained; the plant is very easy to cultivate as is the closely related culinary sage, Salvia officinalis. The extracts and plants contain a series of clerodane diterpenes, typified by salvinorin A (Fig. 19), which is a potent kappa-opioid receptor agonist with activity at doses as low as 200 μg.
Extracts and leaves are typically smoked, although the traditional ethnomedical usage of this plant involved the chewing of the leaves as a ‘quid’ to elicit an effect. A variety of extract strengths are available through internet suppliers, for example, $10 \times$ extract, although as with the case of Kratom, no realistic interpretation of the true concentration of salvinorinA can be made without proper analysis. Users report that they have tried the material once, and have no desire to re-dose as the experience was not particularly pleasant.

**Conclusion**

There are many chemical similarities between ‘legal highs’ and endogenous neurotransmitters, specifically serotonin, norepinephrine and dopamine. Several classes of ‘legal highs’ have been modelled on existing and controlled drugs of abuse, particularly from the phenylethylamine (amphetamine), cocaine, phencyclidine and tryptamine classes. The reason for this is the ease in synthesising these compounds; chemists can readily identify those compounds that fall outside of legislation and are therefore legal, and the routes to these compounds are easily accessible from the literature. The amino-indanes and amino-tetralins (MDAI, MDAT), psychedelic drugs (tryptamines) and anaesthetics (4-MeO-PCP/methoxetamine) are examples that fall outside of existing legislation. There are considerable potential harms associated with taking these ‘legal highs’ as they often have insufficient supporting biological and toxicological data.

**Declaration of interest**

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

**References**

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**Fig. 19.** Salvinorin A, a potent kappa-opioid receptor agonist from the psychedelic sage *Salvia divinorum.*
Clinical experience with and analytical confirmation of “bath salts” and “legal highs” (synthetic cathinones) in the United States

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Recently, there has been a worldwide rise in the popularity and abuse of synthetic cathinones. In 2009 and 2010, a significant rise in the abuse of a new group of synthetic cathinones was reported in Western Europe. In 2010, the rapid emergence of a new drug of abuse, referred to as bath salts or “legal high,” occurred in the USA. The growing number of cases along with the alarming severity of the effects caused by the abuse of these substances prompted significant concern from both healthcare providers and legal authorities. We report the experience of the first 8 months of two regional poison centers after the emergence of a new group of substances of abuse. Method. This was a retrospective case series of patients reported to two poison centers with exposures to bath salts. Additionally, 15 “product samples” were obtained and analyzed for drug content using GC/MS. Results. There were 236 patients of which 184 (78%) were male. Age range was 16–64 years (mean 29 years, SD 9.4). All cases were intentional abuse. There were 37 separate “brand” names identified. Clinical effects were primarily neurological and cardiovascular and included: agitation (n = 194), combative behavior (n = 134), tachycardia (n = 132), hallucinations (n = 94), paranoia (n = 86), confusion (n = 83), chest pain (n = 40), myoclonus (n = 45), hypertension (n = 41), mydriasis (n = 31), CPK elevations (n = 22), hypokalemia (n = 10), and blurred vision (n = 7). Severe medical outcomes included death (n = 1), major (n = 8), and moderate (n = 130). Therapies included benzodiazepines (n = 125), antipsychotics (n = 47), and propofol (n = 10). Primary dispositions of patients were: 116 (49%) treated and released from ED, 50 (21%) admitted to critical care, 29 (12%) admitted to psych, and 28 (12%) lost to follow up. Nineteen patients had blood and/or urine analyzed using GC/MS. MDPV was detected in 13 of 17 live patients (range 24–241 ng/mL, mean 58 ng/mL). The four samples with no drug detected, reported last use of bath salts >20 h prior to presentation. Three of five patients had MDPV detected in urine (range 34–1386 ng/mL, mean 856 ng/mL). No mephedrone or methylone was detected in any sample. Quantitative analysis performed on postmortem samples detected MDPV in blood at 170 ng/mL and in urine at 1400 ng/mL. No other synthetic cathinones were detected. Discussion. This is the first report of MDPV exposures with quantitative blood level confirmation. Clinical effects displayed a sympathomimetic syndrome, including psychotic episodes often requiring sedation, movement disorders, and tachycardia. Within 8 months of their appearance, 16 states had added synthetic cathinones to the controlled substances list as a Schedule I drug. Conclusion. We report the emergence of a new group of substances of abuse in the USA, known as bath salts, with quantitative results in 18 patients. State and federal authorities used timely information from poison centers on the bath salt outbreak during investigations to help track the extent of use and the effects occurring from these new drugs. Close collaboration between state authorities and poison centers enhanced a rapid response, including legislation.

Keywords Synthetic cathinone; Designer drugs; Stimulants; Sympathomimetic syndrome; Drugs of abuse

Introduction

Recently, there has been a worldwide rise in the popularity and abuse of synthetic cathinones. Abuse of one synthetic cathinone – methcathinone – occurred for several decades in the former Soviet Union, Russia, and Eastern Europe and spread to the West in the 1990s.1–3 Methcathinone report-

edly had been developed in the former Soviet Union as an antidepressant in the 1930s and separately developed in the West in the 1950s as an appetite suppressant, but was never marketed due to its strong addictive potential. In 2009 and 2010, a significant rise in the abuse of a new group of synthetic cathinones was reported in Western Europe.4–11 In 2010, the first cases of exposure to products marketed as “legal highs” and bath salts were reported to US poison centers. Based on the increased use in Europe and availability on the Internet for similar “legal highs,” these products were believed to contain various synthetic cathinones, including mephedrone (4-methylenemethcathinone), MDPV...
The product packages were labeled as bath salts, insect repellant, stain remover, and plant food. However, the users of these products openly spoke of using them as “legal methamphetamine” or “legal cocaine.” The product labels did not provide any indication of the true active ingredients. Unlike the European experience, where many of the products were being purchased from a “dealer” or over the Internet, in the USA the majority of the new “bath salt” products were being purchased locally in small independent stores, such as gas stations, smoke shops, and “head shops.”

The growing number of cases along with the alarming severity of the effects caused by the abuse of these substances prompted significant concern from both healthcare providers and legal authorities. During this period in 2010, there was limited information about what these “products” actually contained or the clinical effects that would be expected from abuse of these substances. We report the experience of the first 8 months of two regional poison centers after the emergence of a new group of substances of abuse.

**Methods**

A retrospective search was performed at two poison centers for all records involving what came to be known as bath salts, for the period January 2010 through February 2011. An initial search was performed to locate any case with a substance name listed as bath salts, insect repellant, stain remover, plant food, MDPV, mephedrone, methcathinone, cathinones, white lightning, zoom, blue silk, red dove, ivory wave, white cloud, cloud 9, cloud 10, dynamite, or unknown drug. Poison center case notes were then reviewed to verify if there was documentation that the substances involved an illicit “bath salt” case. In November 2010, both poison centers had agreed to code all these exposures under the term “bath salts.” Product names and descriptions were obtained from the documentation in the case notes. Both centers utilize the electronic medical record system Toxiconcall, which allows review of the record stripped of personal identifiers. All charts were then reviewed by the investigators to verify the substance from the case notes. Calls were received from both the general public and hospitals/healthcare facilities. Toxiconcall allows storage of all calls and consultations on a specific patient in a single medical record, so that each case involved in this study was included only once, despite multiple calls and consultations of many of these patients. Data obtained included age, gender, substance involved, reason for exposure, history of use if obtained, clinical effects, pertinent laboratory values, therapies administered, and medical outcome. Medical outcome designation was the standard American Association of Poison Control Center categories utilized by poison centers.

In a number of cases, because of the confused, agitated, or delusional mental state of the patient, the history of use and any previous abuse history were obtained from significant others of the patient.

During December 2010, because of the lack of information on the contents of these new “products,” 15 products in their sealed original containers were obtained from separate commercial locations (stores) in the two states for analysis of content.

Blood/serum and/or urine waste samples were obtained from 18 patients for analysis as an initial effort to discover what substances might be involved in the toxidrome displayed by the patients. This was part of a public health response to what was considered as an outbreak of a newly emergent substance of abuse. All samples were obtained during initial patient presentation and examination in the emergency department and were obtained after initial clinical use (if any) had been performed.

**Chemicals and reagents**

Analytical reference standards for MDPV, mephedrone, methcathinone, and phencyclidine (the latter two used for internal standards) were obtained from Cerilliant. MDPV was received as the powdered HCI salt. A 1 mg/mL (calculated as the free base) stock solution was prepared from this solution by dissolving 11.3 mg MDPV HCl in 10 mL DI water. Mephedrone, methcathinone, and phencyclidine were received as 1 mg/mL solutions. Blank blood was donated by a local blood bank and determined to be drug free by GC/MS analysis.

**Analysis of purchased products**

After dissolution in methanol, the products were each analyzed using an Agilent 7890A gas chromatograph coupled to an Agilent 5975C mass spectrometer. The column was an Agilent DB-1 (100% dimethylpolysiloxane) (12 m × 0.25 mm × 0.33 μm). Ultra-pure helium was used as the mobile phase using a constant flow of 0.80 mL/min. Other instrumental parameters included: 1 μL injection, split ratio 300:1, injection port 290°C, oven program 100°C for 15 sec, ramped at 65°C/min to 220°C, then at 40°C to 290 with a final hold time of 6.15 min. The total analysis time was 10 min. The mass spectrometer was programmed with a transfer line temperature of 290°C, source temperature of 230°C, quadrupole temperature of 150°C, solvent delay of 0.85 min, and was operated in scan mode from 50 to 550 m/z for the duration of data collection. Identification of the substances present in the bath salts was determined by retention time and mass spectral comparison of the GC/MS data to known standards.

**Quantitation of biological specimens**

For the quantitation of the bath salt drugs in biological specimens, methcathinone and phencyclidine were used as internal standards. The internal standard solution was made by combining 25 μL aliquots of the 1 mg/mL methcathinone and phencyclidine standards and diluting to 25 mL with DI water, resulting in a 1 μg/mL solution for each drug. Similarly, a 1 μg/mL solution containing both mephedrone and MDPV was prepared by diluting 25 μL of each of the 1 mg/mL solutions to 25 mL DI water.

Mephedrone and MDPV calibrators with concentrations of 25, 50, 75, 100, and 150 ng/mL were prepared by pipetting
appropriate volumes of 1 μg/mL solution into 1 mL aliquots of blank blood obtained from a local blood bank and determined to be drug free by GC/MS analysis.

Sample preparation

The calibrators, 1 mL aliquots of biological specimens, and a 1 mL aliquot of blank blood were pipetted into culture tubes and then extracted using the following procedure. Internal standard (50 μL) was added to each sample, followed by 1 mL of borate buffer. After briefly mixing the samples by vortex, 4 mL of n-butyl chloride was added to each sample. Each tube was capped and shaken for 2 min, followed by centrifugation at 3000 rpm for 3 min. After transferring the resulting organic layer to a 5-mL conical centrifuge tube, 2 mL of 1.0 N HCl was added. The conical tubes were capped and placed on a rotary extractor for 15 min, followed by another 3 min centrifugation at 3000 rpm. The organic layer was discarded. Seven drops (approximately 350 μL) of conc. NH₄OH was added to each to basify the aqueous solution. Chloroform (75 μL) was added, and the samples were capped, shaken for 2 min, and centrifuged again at 3000 rpm for 3 min. The resultant chloroform layer was transferred into autosampler vials and then analyzed by GC/MS.

Analysis

Determination of blood concentration and/or urine concentration was performed using another Agilent 7890A/5975C GC/MS. This instrument was equipped with a DB-1 column having dimensions of 30 m × 0.320 mm × 0.25 μm. For biological samples, 2 μL of extract was injected in splitless mode. Other instrumental parameters: injection port 250°C, ultra-pure helium column flow 1.788 mL/min, oven initial temperature 60°C for 1 min, then 15°C/min ramp to 300°C with a hold time of 3 min, total run time 20 min. The mass spectrometer transfer line, source, and quadrupole temperatures were 280, 230, and 150°C, respectively. The mass spectrometer scanned from 40 to 400 m/z after a solvent delay of 3 min.

Results

The first case was reported in August 2010 in Kentucky and the first case in Louisiana occurred in September 2010. From August 2010 through February 2011, there were 236 patients with a rapid escalation in the number of patients reported after November 2010 (see Fig. 1). The majority of patients (n = 184, 78%) were male. The age range was from 16 to 64 years (mean 29 years, SD 9.4). All cases reported the reason for exposure as intentional abuse. Where history was available, a large number of cases reported previous abuse of methamphetamine and/or cocaine and the use of bath salts as a “legal” replacement for these substances. Results from qualitative urine drug screens were recorded in 44 patients and detected positive results for amphetamines, barbiturates, benzodiazepines, caffeine, cannabinoids, cocaine, MDMA, methadone, opiates, oxycodone, and oxymorphone. There were 39 separate “brand” names identified from patient histories (Table 1). In 72% of cases, the originating contact call was from the hospital, with 6% originating from EMS/ambulance service and 22% from the public.

Clinical effects were primarily neurological and cardiovascular and are reported in Table 2. Severe medical outcomes included: death (n = 1), major (n = 8), and moderate (n = 130). The single fatality occurred in a 21-year-old male from a self-inflicted gunshot after an active delusional episode witnessed by family members. A number of alarming and dangerous behaviors (to either self or others) were reported in these patients in temporal association with acute use of large amounts or prolonged use of “bath salts” over several days to several weeks. Examples of these new onset behaviors in separate patients included: jumping out of a window to flee from non-existent pursuers; requiring electrical shock (Taser) and eight responders to initially subdue the patient; repeatedly firing guns out of the house windows at “strangers” who were not there; walking into a river in January to look for a friend who was not there; leaving a 2-year-old daughter in the middle of a highway because she had demons; climbing into the attic of the home with a gun to kill demons that were hiding there, and breaking all the windows in a house and wandering barefoot through the broken glass.

Therapies were primarily sedation and treatment for persistent myoclonus and included the benzodiazepines diazepam, lorazepam, and/or midazolam (n = 125, 53%), the antipsychotics haloperidol and ziprasidone (n = 47, 20%), propofol (n = 10, 4%), and diphenhydramine (n = 2, 1%). The dispositions of patients were: 116 (49%) treated and released from the emergency department, 50 (21%) admitted to a critical care unit, 29 (12%) admitted to behavioral health/psychiatry, 28 (12%) were lost to follow up, and 13 (6%) were managed at a non-healthcare facility.

Eighteen live patients had blood and/or urine analyzed using GC/MS. MDPV was detected in the blood/serum of 13 of 17 patients (range 24–241 ng/mL, mean 58 ng/mL).
The four samples with no synthetic cathinone detected, reported last use of bath salts >20 h prior to presentation. Additional drugs detected in the blood/serum included citralopram, diazepam, diphenhydramine, hydrocodone, and zolpidem. Three of five patients had MDPV detected in urine (range 34–1386 ng/mL, mean 856 ng/mL). Additional drugs detected in the urine were alprazolam, citalopram, diazepam, diphenhydramine, hydrocodone, and methamphetamine. No mephedrone or methylone was detected in any sample. Ethanol detection was not included in analysis. Quantitative analysis was performed on postmortem samples in the single fatality. MDPV was detected in blood at 170 ng/mL and in urine at 1400 ng/mL. No other synthetic cathinones were detected.

Fifteen products in their sealed original containers were obtained from separate locations in the two states. The products contained one or more of three of the known synthetic cathinones: 4-methylmethcathinone (mephedrone), methylenedioxypyrovalerone (MDPV), or 4-methylenedioxy-N-methylcathinone (methylone). Additional substances found included caffeine and an unidentified substance (see Table 3).

Table 1. Names of products reported by users.

<table>
<thead>
<tr>
<th>Product name</th>
<th>Frequency of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artic blasting station</td>
<td>1</td>
</tr>
<tr>
<td>Atomic</td>
<td>1</td>
</tr>
<tr>
<td>Bayou revitalisant</td>
<td>1</td>
</tr>
<tr>
<td>Blaze</td>
<td>1</td>
</tr>
<tr>
<td>Blitz</td>
<td>2</td>
</tr>
<tr>
<td>Blue moon</td>
<td>1</td>
</tr>
<tr>
<td>Blue silk</td>
<td>5</td>
</tr>
<tr>
<td>Bohemian bath salts</td>
<td>2</td>
</tr>
<tr>
<td>Bolivian bath salts</td>
<td>2</td>
</tr>
<tr>
<td>Dr. booga shooga</td>
<td>3</td>
</tr>
<tr>
<td>Cloud 9</td>
<td>73</td>
</tr>
<tr>
<td>Cloud 10</td>
<td>2</td>
</tr>
<tr>
<td>Columbian odorizer</td>
<td>1</td>
</tr>
<tr>
<td>Cotton cloud</td>
<td>4</td>
</tr>
<tr>
<td>Dream</td>
<td>1</td>
</tr>
<tr>
<td>Dynamite</td>
<td>1</td>
</tr>
<tr>
<td>Euphoria</td>
<td>1</td>
</tr>
<tr>
<td>Hurricane charlie</td>
<td>1</td>
</tr>
<tr>
<td>Ivory wave</td>
<td>9</td>
</tr>
<tr>
<td>Ivory wave ultra</td>
<td>1</td>
</tr>
<tr>
<td>Kush blitz</td>
<td>1</td>
</tr>
<tr>
<td>Lady bubbles</td>
<td>2</td>
</tr>
<tr>
<td>Legal</td>
<td>2</td>
</tr>
<tr>
<td>Love potion 69</td>
<td>2</td>
</tr>
<tr>
<td>Moon dust</td>
<td>4</td>
</tr>
<tr>
<td>Night cap</td>
<td>1</td>
</tr>
<tr>
<td>NRG-l</td>
<td>1</td>
</tr>
<tr>
<td>Q concentrated</td>
<td>1</td>
</tr>
<tr>
<td>Red dove</td>
<td>1</td>
</tr>
<tr>
<td>Resin</td>
<td>1</td>
</tr>
<tr>
<td>Scar face</td>
<td>1</td>
</tr>
<tr>
<td>Serenity</td>
<td>1</td>
</tr>
<tr>
<td>Super clean stain remover</td>
<td>1</td>
</tr>
<tr>
<td>White cloud</td>
<td>1</td>
</tr>
<tr>
<td>White diamonds</td>
<td>2</td>
</tr>
<tr>
<td>White dove</td>
<td>1</td>
</tr>
<tr>
<td>White girls bath salts</td>
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<td>White lightening</td>
<td>24</td>
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<td>Zoom</td>
<td>6</td>
</tr>
</tbody>
</table>

Discussion

We report the largest series of synthetic cathinone exposures with a number of important features, including a high incidence of new onset severe neurological/psychiatric changes; qualitative results of the contents of “bath salts”; and quantitative results of blood and urine in synthetic cathinone users.

Previous reports of synthetic cathinone use/abuse have focused primarily on mephedrone and have reported clinical effects consistent with a sympathomimetic syndrome, including tachycardia, agitation, hypertension, palpitations, chest pain, confusion, paranoia, hallucinations, violent behavior, and seizure. Our results are consistent with these previous reports. However, in our case series, we found aggressive violent behavior, hallucinations, and paranoia in higher percentages than previously reported. It is interesting to note that the high incidence of neurological/psychiatric changes occurred in a population that had pre-existing experience with illicit stimulant abuse, such as cocaine and methamphetamine, who had not previously reported episodes of neurological/psychiatric changes of such severity. The increased incidence may have occurred for a number of reasons. Experience with misuse/abuse of this drug is limited. While the reported incidence pattern is different from previous reports of synthetic cathinone abuse, the clinical effects reported are similar, and this may simply be a reflection of a difference in dosing patterns or patient populations (e.g. “club” drug use vs. street drug abuse). Another possibility is that this may represent a difference in clinical patterns from the individual synthetic cathinones, perhaps based on subtle differences in the effects on neurotransmitters. The previous reports from the European experience primarily involved mephedrone. However, in our case series, all verified serum or urine samples contained MDPV, with no detected mephedrone or methylone. This second possibility should be viewed with caution as only 6% of patients in our series had laboratory verification of their exposure. Movement disorders may also be a differentiating factor. A previously unreported finding in our series was myoclonus in 19% of the patients and elevated CPK in 9% of the patients. One report of “ivory wave” exposure, which may have involved MDPV, reported involuntary facial contortions, supporting a possible movement disorder as a clinical effect with MDPV abuse. Previous reports of a parkinsonian syndrome associated with methcathinone have been attributed to a manganese contamination during illicit preparation of the drug.

Analysis of the “legal high” or “bath salt” products revealed a combination of three synthetic cathinones: mephedrone, methylone, and MDPV. This is similar to the European experience, with some differences. In the USA, the primary synthetic cathinone available was not mephedrone, and the main distribution point was through small local stores. We believe that the wide availability, coupled with the ease of anonymous local purchase and inexpensive.
products, allowed a rapid expansion of these drugs into the market. In many cases, they were easier to obtain than beer or cigarettes. Additionally, no ingredients were listed on the packaging. Unlike web sites that may allude to ingredients that the knowledgeable prospective customer might recognize and/or desire, the bath salt products were primarily sold in small stores by clerks with little or no knowledge of what the product might contain. Analysis of two "brand names" (white lightening and dynamite), which were obtained at different locations, revealed different synthetic cathinones as the primary ingredient, despite similar appearing packaging. The 15 products analyzed and reported here were purchased in December 2010 and may not represent the psychoactive substances in future "bath salt" or "legal high" products. A wide variety of novel psychoactive substances are available and may replace the substances detected in the present group of products.12,24

Quantitative analysis showed serum levels of 24–241 ng/mL of MPV. Previous serum MDPV concentrations in live patients have not been reported, but these concentrations are in the range of the mephedrone level (0.15 mg/L) reported by Wood et al.20 A limitation of interpreting these blood/serum levels of MDPV is that the time from use of the drug to the time of obtaining the sample is not known. We believe this is the first report of postmortem quantitative MDPV concentrations. Postmortem concentrations in five fatalities associated with another synthetic cathinone, mephedrone, ranged from 0.13 to 5.1 mg/L.4,5 Urine concentrations after abuse of MDPV have recently been reported in Finland in a group of opioid-dependent patients undergoing opioid substitution therapy.21 The similarities between our patient group and the report by Ojanpera et al. were the reported use of MDPV as a substitute for illicit amphetamine and similar urine concentrations. This suggests that urine may be a useful medium to detect previous MDPV abuse.

Table 2. Reported clinical effects.

<table>
<thead>
<tr>
<th>Clinical effect</th>
<th>No. of patients with reported effect (% of total patient group)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>194 (82%)</td>
<td>Mean heart rate for those with reported tachycardia was 124 (SD 15.5) with a range of 100–178 beats per minute</td>
</tr>
<tr>
<td>Combative violent behavior</td>
<td>134 (57%)</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>132 (56%)</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>94 (40%)</td>
<td></td>
</tr>
<tr>
<td>Paranoia</td>
<td>86 (36%)</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>83 (34%)</td>
<td></td>
</tr>
<tr>
<td>Myoclonus</td>
<td>45 (19%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (17%)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>40 (17%)</td>
<td></td>
</tr>
<tr>
<td>Mydriasis</td>
<td>31 (13%)</td>
<td></td>
</tr>
<tr>
<td>CPK elevations</td>
<td>22 (9%)</td>
<td>Mean reported CPK elevation was 1825 U/L with a range of 301–4400 U/L</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>10 (4%)</td>
<td>Mean reported potassium for those with hypokalemia was 2.9 mEq/L with a range of 2.1–3.4 mEq/L</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>7 (3%)</td>
<td></td>
</tr>
<tr>
<td>Catatonia</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

Definitions: Tachycardia was a heart rate >99 bpm; hypertension was systolic pressure >170 mmHg or diastolic pressure >90 mmHg; hypokalemia K <3.5 mEq/L, CK elevation CPK >250 U/L.

Table 3. Ingredients detected in “bath salt” samples.

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug found</th>
<th>Labeled “use”</th>
<th>Physical appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>White lightening</td>
<td>Mephedrone</td>
<td>Insect repellent</td>
<td>White dry powder</td>
</tr>
<tr>
<td>White lightening</td>
<td>MDPV</td>
<td>Natural stain remover</td>
<td>White dry powder</td>
</tr>
<tr>
<td>Zoom</td>
<td>MDPV</td>
<td>Bath salt</td>
<td>Beige powder</td>
</tr>
<tr>
<td>Energizing aromatherapy powder</td>
<td>MDPV and caffeine</td>
<td>Potpourri</td>
<td>Beige powder</td>
</tr>
<tr>
<td>Euphoria</td>
<td>Methyline and caffeine</td>
<td>Bath salt</td>
<td>Beige powder</td>
</tr>
<tr>
<td>Cotton cloud</td>
<td>Mephedrone, methylene, and MDPV</td>
<td>Bath salt</td>
<td>White crystalline powder</td>
</tr>
<tr>
<td>Cloud 9</td>
<td>Methylene and MDPV</td>
<td>Bath salt</td>
<td>Beige powder</td>
</tr>
<tr>
<td>Bayou ivory flower</td>
<td>Mephedrone</td>
<td>Bath salt</td>
<td>Beige powder</td>
</tr>
<tr>
<td>Cloud 10</td>
<td>MDPV</td>
<td>Not on product</td>
<td>Beige powder</td>
</tr>
<tr>
<td>White dove</td>
<td>Methyline</td>
<td>Bath salt</td>
<td>Beige powder</td>
</tr>
<tr>
<td>Dynamite</td>
<td>Methyline</td>
<td>Bath salt</td>
<td>White dry powder</td>
</tr>
<tr>
<td>Dynamite “plus”</td>
<td>MDPV</td>
<td>Bath salt</td>
<td>Beige powder</td>
</tr>
<tr>
<td>White china</td>
<td>MDPV and unknown compound</td>
<td>Bath salt</td>
<td>Beige powder</td>
</tr>
<tr>
<td>Snow day</td>
<td>Methyline and MDPV</td>
<td>Bath salt</td>
<td>Beige powder</td>
</tr>
<tr>
<td>Bolivian bath salts (scarface)</td>
<td>MDPV</td>
<td>Bath salt</td>
<td>White dry powder</td>
</tr>
</tbody>
</table>
Little is known of the mechanism of action of synthetic cathinones, but a clinical picture of a sympathomimetic syndrome has become evident. Methcathinone and methylone appear to inhibit membrane catecholamine transporters, suggesting a reuptake inhibition. Comparison of methcathinone and methylone to methamphetamine and methylenedioxymethamphetamine (MDMA) showed similar effects on dopamine and norepinephrine reuptake inhibition, but methylone with its 3,4-methylenedioxy group showed increased serotonin reuptake inhibition.15 Animal studies with methylone showed potent monoamine release effects for dopamine and serotonin and less so for norepinephrine, and reflected reuptake inhibition of dopamine, norepinephrine, and serotonin.16 In a mouse model, MDPV increased dopamine concentrations but did not appear to affect serotonin concentrations.17 While the mechanism is not yet fully elucidated, it appears that the behavioral toxicity (including self-injurious behavior and schizophrenic-like psychoses) and movement disorders of synthetic cathinones may have a dopaminergic mechanism similar to amphetamines.22,23

Within 8 months of their appearance on the US market, more than 1400 cases of misuse and abuse of “bath salts” had been reported to US poison centers in 47 of 50 states. On 6 January 2011, Louisiana passed an emergency rule placing six synthetic cathinones in Schedule I. The substances banned were 3,4-methylenedioxymethcathinone (methylene), 3,4-methylenedioxyxypovalerone (MDPV), 4-methylmethcathinone (mephedrone), 4-methoxymethcathinone (methedrone), 3-fluromethcathinone, and 4-fluoromethcathinone (flephedrone). The number of cases reported in Louisiana decreased dramatically after the ban was put in place on 6 January 2011 (Fig. 1). Within 3 months of this, 15 more states added synthetic cathinones to the controlled substances list as Schedule I drugs, either through temporary emergency rule or direct legislation (Kentucky, Alabama, Arkansas, Florida, Hawaii, Illinois, Idaho, Mississippi, North Dakota, Oregon, Utah, Virginia, Washington, Wisconsin, and Wyoming). Legislation is pending in a number of additional states. Timely information from poison centers on the bath salt outbreak was used by state and federal authorities during investigations to help track the extent of use and effects occurring from these new drugs. Close collaboration between state authorities and poison centers enhanced a rapid response, including legislation.

**Conclusion**

We report the emergence of a new group of substances of abuse in the USA, known as bath salts, with quantitative results of MDPV use in 19 patients. Calls to US poison centers as a result of the use and abuse of these drugs were first noted in 2010. Rapid analysis and identification of the synthetic cathinones involved in these substances as well as the coordinated response by two poison control centers have permitted a picture of this new epidemic to be presented. The growing number of cases together with the alarming severity of the effects caused by the abuse of these substances prompted significant concern from both healthcare providers and legal authorities. Since the emergence of these bath salts, a growing number of states have designated six synthetic cathinones as Schedule I controlled substances. However, there are a large number of potential novel psychoactive “designer” drugs that may possibly be distributed in the future.24 Changes to specific moieties may not be addressed in the current legislation, leaving clinical toxicologists, poison centers, and emergency physicians to face an on-going pattern of chasing the next ivory wave.

**Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**References**


