The use of Synthetic Cathinones and Tryptamines in a Psychiatric Population

LJ Reidy*, P Junquera*, KR Van Dijck†, BW Steele‡ and Ihsan M Salloum*

Abstract

A new wave of designer drugs is emerging in both emergency room (ER) patients and the community at large. These drugs are a synthetic modification of the naturally occurring alkaloid cathinone, which can be extracted from the leaves of Catha edulis, commonly known as the khat plant. The synthetic cathinones such as methylone; 3, 4 methylenedioxyprovalerone (MDPV); mephedrone; and ethylone are commercially sold under various names such as "Ivory Wave", "Vanilla Sky" and "Bliss". The tryptamines discussed in this paper are a group of psychedelic substances primarily regarded for their hallucinogenic properties. Commonly known tryptamines include LSD and psilocybin found in magic mushroom. Less commonly known tryptamines such as DMT, AMT and 5MEODiPT are the compounds of interest in this paper.

Routine drug toxicology screens do not test for these drugs, thus missing a potential cause for psychotic symptoms, which may lead to missed diagnosis and inappropriate treatment. This paper describes three admissions into a hospital for psychiatric treatment with a negative routine toxicology test. This study reveals that with more advanced toxicology testing the identification of one or more of these new designer "bath salts" and or synthetic tryptamines were appropriate in these cases. This paper describes the emerging trend in use of this type of drugs and consequently our findings highlights the importance of performing laboratory test that are able to identify these drugs to help in appropriate diagnosis and treatment of patients presenting with suspected psychiatric disorders.

Introduction

A new wave of designer drugs is emerging in both emergency room (ER) patients and the community at large and can be referred to as "novel psychoactive substances" (NPS). One group of substances is the synthetic cathinones which are sold commercially as "bath salts". These drugs produce physiological toxic effects as well as disturbing psychopathological symptoms. These drugs are commonly the synthetic modification of the naturally occurring alkaloid cathinone, which can be extracted from the leaves of Catha edulis, (khat plant) [1]. The synthetic cathinones such as methylone; mephedrone; ethylone; and 3, 4 methylenedioxyprovalerone (MDPV); (Figure 1) are frequently sold under various names such as "Ivory Wave", "Vanilla Sky" and "Bliss" in head shops and gas stations.

The prevalence of use of these drugs is likely to be largely underestimated due to the lack of testing and to the perception of unavailability of testing methodologies. The American Association of Poison Control Centers (AAPCC) reported a dramatic increase of bath salt related calls from 303 calls in 2010 to 6,072 calls in 2011 [2].

These drugs have amphetamines-like effects and user report a likeness to both 3, 4-methylenedioxy-N-methylamphetamine (MDMA) and to cocaine. They enhance the synaptic activation of biogenic amines such as norephinephrine, dopamine and serotonin either by inhibiting their re-uptake, or by stimulating their release from storage vesicles [3]. Users report a variety of psychedelic effects including a sense of well being, a sense of profound insight and introspection, closed and open eyed visuals, increased appreciation of music and empathogenicity. Effects on the body include increased blood pressure, blurred vision, dehydration, nausea, vomiting, dilated pupils and tachycardia. The observed peripheral cardiovascular effects are largely due to norephinephrine that is also thought to contribute to the alerting, locomotor stimulation and anorexic effects seen with these drugs [4].

The development of psychosis and hallucinations has been attributed to the effects of serotonin. The development of psychosis may require the intake of high doses as some of these NPS have a smaller ability to inhibit the re-uptake of serotonin and have shown a decreased affinity for VMAT2 (vesicular monoamine transporter).
The second NPS group described in this paper is the tryptamines. Tryptamines are well known for their psychoactive properties and have been used for centuries, especially in the context of religious rituals and folk medicine [6]. The tryptamines discussed in this paper are a group of psychedelic substances primarily regarded for their hallucinogenic properties. Tryptamines are found naturally in plants for example N,N-Dimethyltryptamine (DMT), the active component of the ayahuasca brews often derived from the chacruna plant, fungi (e.g psilocybin from “magic mushrooms”) and animals (Bufotenin or 5-hydroxy-N,N-dimethyltryptamine from the (Bufo alvarius toad) . Commonly known tryptamines include Lysergic Acid Diethylamide (LSD) and psilocybin. However, there are also many synthetic tryptamines such as dipropyltryptamine (DPT), AMT and 5-methoxy-diisopropyltryptamine (5-MeO-DiPT). This group of compounds has been extensively studied and described in Alexander Shulgin’s TIKHAL (Tryptamines I Have Known and Loved) [7]. The internet has facilitated the illicit use of these various tryptamines and synthetic cathinones in recent years. Various web sites offer information on where to buy these drugs and about where to find plants that naturally contain a tryptamines and how to extract them [6]. Effects of some of these tryptamines include euphoria, dilated pupils, empathy, nausea, vomiting and diarrhea [8,9].

There are limited published articles on the specific pharmacology or toxicology of most of these new psychedelic compounds in humans. Hadlock et al. [10] demonstrated that mephedrone has a unique pharmacological profile different from MDMA known on the streets as ‘ecstasy’ or ‘molly’ and from methamphetamine. Mephedrone has been shown to cause greater dopamine (DA) release than MDMA; hence it may have higher abuse liability [11]. Information regarding synthetic cathinone abuse liability and neurotoxin potential are generally lacking in regards to mephedrone and methylene. Winsock et al. [12] determined after compiling an online survey that mephedrone had similar abuse potential to cocaine.

These recreational drugs are not routinely tested by clinical laboratories due to financial constraints, analytical capabilities and time limitations. Thus, the presence and the rate of these drugs in patients presenting for care is still largely unexplored. This is especially true for patients presenting for psychiatric care, as it is unclear how many of those presenting for psychiatric care may be wrongly diagnosed with primary psychotic disorder while their symptoms may be due to the abuse of these substances. It is also unclear how frequent the abuse of these drugs among psychiatric patients in general and what is the impact of their use on symptoms exacerbation and emergency use care for this population. We conducted a simple and efficient urine drug screen aimed at identifying the presence and incidence level of these “designer drugs” in an inner-city, psychiatric department.

**Study Design**

This protocol was approved by the Institutional Review Board (IRB) of the University of Miami. The study samples consisted of 209 consecutive patients who were admitted to the inpatient detoxification unit of an inner-city community hospital over a three month period that provided a urine sample. Patients were tested by routine clinical toxicology methods at the hospital laboratory and then subsequently re-analyzed at the toxicology laboratory at the University of Miami. The sample group was comprised of 71% males and 29% females, 19% of them were between the ages 18-25, and 34% were between 25-40 and the remainder over 40 years old. We were provided with de-identified samples with patient demographics (age and gender), clinical toxicology results and clinical diagnosis. The clinical toxicology screen was carried out by Enzyme Immunosorbant Assay (EIA) screening for five drug groups; amphetamines; cannabis; cocaine; opiates and benzodiazepines.

**Toxicology Analysis**

**Apparatus**

Gas chromatography-Mass spectrometry (GC-MS) analysis was performed on an Agilent 7890 GC coupled to a 5975 MS. The mass selective detector operated in electron impact mode. The electron multiplier was set 200 volts relative to the auto tune value. The GC was fitted with a Agilent column (15 M x 0.25 mm i.d x 0.25 μm d.f.) fitted with a deep switch operating in split less mode (bottom gooseneck liner with no glass wool) with helium as the carrier gas operated in constant pressure mode at 31.49 psi with an injection volume of 1 μL. The injector and detector temperatures were 280°C and 300°C, respectively. The initial oven temperature was held at 100°C for 0.5 min, and then ramped at 40°C/min to 325°C with a hold time of 2 min (total run time 7 min). The GC is fitted with two detectors, a nitrogen phosphorous detector (NPD) and mass spectrometer (MS).

The MS was operated in the full scan mode (40–600 amu) and data was acquired and analyzed using Agilent ChemStation software version G1761 AA revision no: E02.02 and Agilent DRS software G1716 AA revision no: A04.00 (Santa Clara, CA) and running the AMDIS deconvolution software using a library of over 750 compounds.

**Chemicals**

Methylenedioxymethamphetamine (MDMA), mephedrone, buphedrone, methcathinone and prazepam, were purchased from Cerilliant Corporation (Round Rock, TX). DPT, DMT, 5-methoxy-α-methyltryptamine (5-MeO-αMT), 5-methoxy-diisopropyltryptamine (5-MeO-DiPT), 5-methoxy- N,N-Dimethyltryptamine (5-MeO-DMT), N-propylamphetamine, ethyl morphine, cyclizine were purchased from Altech (Deerfield, IL). All solvents were Sigma Aldrich (Sigma-Aldrich Co. LLC St. Louis, MO) HPLC-grade or equivalent.

**Analysis protocol**

All samples were extracted using a Basic Drug Screen (BDS) and subjected to gas chromatography mass spectral (GC-MS) analysis. This is a quick extraction and able to quantify a large number of these synthetic drugs. Individual stock standards of methylene, MDPV, ethylone, and various tryptamines were analyzed via GC-MS to determine the mass spectral profile, retention time. The Limit of Detection (LOD) was established using the United Nations Office on Drugs and Crime (UNODC) guidelines.

**BDS By GC-MS**

The GC-MS screening for drugs in urine was conducted with an alkaline liquid-liquid extraction, with modifications to the published procedure by Forester et al. [13]. Briefly, urine aliquots (2 mL) were
dispensed into 17 mL silanized screw cap tubes. The internal standard (m-propylamphetamine, citalopram, ethyl morphine, prazepam) was added to each tube of urine to give a final concentration of 500 ng/mL. To each tube 9 mL of n-butyl chloride: methylene chloride (9:1) was added and briefly vortexed. 1 mL of concentrated ammonium hydroxide (33%) was added to each tube, and the tube was sealed with a Teflon lined cap. The samples were then extracted on a rotor rack for 15 min. Tubes were centrifuged at 3800 rpm for 10 min at -10°C to produce separation and the organic layer transferred to a silanized conical tube and evaporated to just dryness in a TurboVap® at 50°C under a stream of nitrogen. The dry urine extract was reconstituted with 50 μL isooctane: methylene chloride: ethanol (7:2:1); and subsequently transferred to limited volume auto-sampler vials; and analyzed via GC-MS in scan mode. Positive and negative controls were prepared in-house and interferences were investigated by running blank and negative urine controls.

Results

The results of the drug fortified urine samples are presented in Table 1. Methylole and ethylone yielded similar mass spectra data; however they were separated based upon their respective retention times. The limit of detection (LOD) for the synthetic cathinones was 50 ng/mL and the LOD for the tryptamines compounds was 25 ng/mL.

Three patients from the 209 samples analyzed confirmed positive for one or more of these synthetic compounds. We present the clinical and toxicological data for each patient below.

Patient 1

Patient 1 was a male aged 33 yr who presented to the psychiatric emergency department with severe stomach discomfort and alcohol intoxication. Admission toxicology testing by the hospital toxicology laboratory reported a presumptive positive for amphetamines (class) drug and negative for 4 other immunoassays (cocaine metabolite, opiates, benzodiazepines, cannabinoids). Urine analysis test by ELISA screened positive for amphetamine (class), methamphetamine/MDMA (class) and confirmed positive results for amphetamine, methamphetamine, venlafaxine and metabolites. More interestingly, it also confirmed positive by GC/MS for 5-Me-O-DiPT and DPT. In a typical clinical laboratory testing, the drugs in the tryptamines family would not have been identified, as a commercial ELISA or EIA kit typical clinical laboratory testing, the drugs in the tryptamines family it also confirmed positive by GC/MS for 5-Me-O-DiPT and DPT. In a

Table 1: Identification criteria and sensitivity data for a series of synthetic cathinones and tryptamines using an alkaline liquid extraction and GC-MS.

<table>
<thead>
<tr>
<th>Compound/Drug</th>
<th>Limit of detection (ng/mL)</th>
<th>Retention time</th>
<th>Main Mass Spectrometry fragments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mephedrone</td>
<td>50</td>
<td>1.90</td>
<td>58, 91, 119, 162</td>
</tr>
<tr>
<td>Methylole</td>
<td>50</td>
<td>2.68</td>
<td>58, 91, 121, 149</td>
</tr>
<tr>
<td>Ethylone</td>
<td>50</td>
<td>2.85</td>
<td>72, 121, 149, 44, 243</td>
</tr>
<tr>
<td>Buphedrone</td>
<td>50</td>
<td>1.73</td>
<td>72, 44, 105, 148</td>
</tr>
<tr>
<td>Methcathinone</td>
<td>25</td>
<td>1.51</td>
<td>58, 81, 148</td>
</tr>
<tr>
<td>Dipropyltryptamine</td>
<td>25</td>
<td>3.72</td>
<td>114, 144, 169,86,43,125</td>
</tr>
<tr>
<td>5-ME-MPT (5-methoxy-alpha-methyltryptamine)</td>
<td>25</td>
<td>3.48</td>
<td>161, 117, 89, 44, 204,144</td>
</tr>
<tr>
<td>5-Methoxy-dipropyltryptamine</td>
<td>25</td>
<td>3.94</td>
<td>86, 117, 160, 246, 215, 44</td>
</tr>
</tbody>
</table>

Discussion

Out of the 209 urine samples tested, 3 samples (1.5%) were positive for one or more of these NPS compounds that would have been missed by a routine clinical laboratory. This study only measured some of the synthetic cathinones and tryptamines, with the inclusion of some other NPS such as the synthetic cannabinoids, PCP similar drugs etc, and 1.5% may be an underestimation of the use of NPS in this population. Previous papers detailing the effects of these new designer drugs on patients has been largely focused on patients admission to using one or more of these drugs [4]. This is the first paper, to the author’s knowledge, that correlates the toxicology with the admission findings of four different compounds. Recent papers have identified mephedrone as the drug of choice in “bath salt” preparation [14] however in this study methylole the only “bath salt” was found in these samples.

While only 1.5% was positive for the NPS tested for in this study, each case highlights an important argument to attempt to include these tests in routine emergency room screen. This is largely attributed to the profound psychological effects that these drugs may have on an individual. The potential etiology of patient 1 gastrointestinal distress would have been completely missed using routine urine screening tests. The results obtained in patient 2 clearly raises the question of whether the psychiatric diagnosis of bipolar disorder is correct and whether the psychiatric symptoms presenting for this patient are all due to this previously unrecognized drug use. If this patient has a verified bipolar diagnosis, it is unclear how much this diagnosis was exacerbated by the use of these drugs as well. Similar questions are raised by patient 3.

Whilst identification of these NPS’s may not aid in the acute management of the patients, there is long-term implication and patient management. The implications of a misdiagnosis could be far
reaching. Usually a diagnosis of bipolar disorder or of schizophrenia requires life-long treatment with psychotropic medications. Therefore, the ability to rule out drug induced symptoms is crucial for the long term care for these patients. It is equally important for the care of patients with chronic psychiatric disorders is the ability to identify precipitating and exacerbating factors, most frequent among them is unrecognized substance abuse. The pharmacodynamics effects of these amphetamine-like drugs produce symptoms that mimic both psychosis and mania. These drugs also exacerbate these manic, psychotic and other mood symptoms in patients who suffer from these disorders. The alkaline extract analysis by GC-MS is comprehensive, quick and cost effective urine toxicology which helps to clarify the presenting diagnostic picture, which is a crucial first step for implementing effective treatment plans. Typically drugs screens are thought of as immunoassay, which in the author’s opinion and are too targeted and expensive. However by utilizing GC-MS, the cost can be reduced to about $100 for analysis of over 750 compounds in one analysis so therefore is extremely cost effective. With advancements in automatic reporting of drugs with known mass spectra ID and the cost of instrumentation vastly reduced to similar cost of an automated immunoassay analyzer this method is becoming more applicable in clinical setting. With the development of LC-MS-MS screening this cost can be reduced further again as sample preparation is less time consuming and labor intensive enabling this type of testing as a potential tool for clinicians.

Limitations of this study include its pilot exploratory nature and the nature of the population tested which may limit its generalizability to other settings or patient populations. The results of this study however, highlight the need for larger studies to systematically assess the frequency and impact of “designer drugs” use on patients presenting for psychiatric care.

The impact that these “new” designer drugs are having on a community as a whole is largely unknown at this point. The long term negative outcomes such as cognitive impairment, drug dependence and mental health disorders, associated with the use of tryptamines and synthetic cathinones are unknown. Cognitive impairment and neurological toxicity impairment for instance has been associated with the more common tryptamines and phenethylamines such as MDMA and LSD, although these studies are somewhat disputed [15,16]. Patients with psychiatric disorders may be more at risk of having a psychotic episode when using these drugs. This paper highlights the need for comprehensive toxicology testing when treating psychiatric patients as the presentation of their symptoms and behavior may not be due to a schizophrenic or psychotic episode but may be due to drug use. With only conventional hospital toxicology testing there may be a considerable lack of toxicology information which may alter the way a patient is treated.

References


Author Affiliations

1. University of Miami, Department of Pathology, University of Miami Forensic Toxicology Laboratory, Florida, USA
2. University of Miami, Department of Psychiatry and Behavioral sciences, USA

Submit your next manuscript and get advantages of SciTechnol

Submit your next manuscript at www.sciotechnol.com/submission