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Review

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Review

Reports of Adverse Events Associated with Use of Novel Psychoactive Substances, 2013–2016: A Review

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Abstract

Novel psychoactive substances (NPS) represent significant analytical and interpretive challenges to forensic and clinical toxicologists. Timely access to case reports and reports of adverse incidents of impairment or toxicity is imperative to clinical diagnosis and treatment, as well as to interpretation of forensic results. Delays in identifying the presence of a novel intoxicating agent have significant consequences for public health and public safety. Adverse effects of intoxications with novel cannabinoids, stimulants, hallucinogens, benzodiazepines and opioids spanning January 2013 through December 2016 as reported in emergency departments, death investigations, impaired driving cases and other forensic contexts are the subject of this review. Discussion of the chemistry, pharmacology and adverse events associated with novel drug classes is summarized and described within. Adverse effects or symptoms associated with ingestion of more than 45 NPS have been abstracted and summarized in tables, including demographics, case history, clinical or behavioral symptoms, autopsy findings and drug confirmations with quantitative results when provided. Based on these findings and gaps in the available data, we provide recommendations for future toxicological testing of these evolving substances. These include development and management of a national monitoring program to provide real-time clinical and toxicological data, confirmed analytically, on emerging drugs and their known toxidromes and side effect profiles. Increased efforts should be made to analytically confirm the agents responsible for clinical intoxications involving adverse events in emergency department admissions or hospitalizations. Evidence-based community preparedness among analytical laboratories gained through active communication and sharing of toxicological findings and trends in NPS is imperative to assist in enabling early detection of new drugs in forensic and clinical populations.

Introduction

Novel psychoactive substances (NPS), commonly described as novel, designer or synthetic drugs, have rapidly increased in popularity and notoriety in recent years, most recently relating to the designer opioid crisis. The term designer drug was originally used to characterize heroin-like derivatives, such as the fentanyl analogues, but gained circulation with the increased popularity of MDMA (1). Since that time in the early 1980s, hundreds of NPS have been

synthesized and introduced onto the drug market nationally and internationally. Synthesis of NPS has been facilitated by pharmaceutical companies researching new drugs for therapeutic value, but these drugs have been pirated from medical journals, scientific literature or patent filings and clandestinely manufactured for illicit use (2). Often the motivation in producing these novel substances is in an attempt to circumvent drug laws or government scheduling (3).

Over a decade ago, the onslaught of synthetic chemical substances hitting the drug market became unprecedented, notably through Internet offerings to imitate and heighten the effects of classical drugs. The increase in availability and turnover quickly surpassed historical drug market capabilities as it became evident that the drug suppliers were heavily equipped with adept synthetic chemists and advanced chemical capabilities. By 2005, the European Community adopted the term of "new psychoactive substances," defined as unscheduled "narcotic or psychotropic drugs … which may pose a threat to public health comparable to scheduled substances" (4). By definition, NPS are not necessarily newly developed drugs, and can constitute emerging or unscheduled drugs recently appearing in the drug market. The identification of new substances requires analytical prowess, often allotting to added time, needed expertise and increased cost.

Review of the literature is critical to our understanding of the drug market, adverse events and analytical challenges. While there is a growing body of literature on NPS, publications involving adverse events can be limited in information, dispersed between multiple publications or journals, and absent of analytical confirmation. Older NPS reviews provide evidence of the changing drug market and challenges facing clinical and forensic laboratories (4, 5). Review articles in more recent years cover in-depth the history, chemistry and pharmacology of NPS in general (6), synthetic cannabinoids (7, 8), designer stimulants (9) and novel hallucinogens (10), and few have reported adverse events associated with NPS ingestion (9, 11, 12). A comprehensive review of the adverse events associated with the most current NPS is lacking.

NPS represent significant challenges to forensic and clinical toxicologists in several arenas. Case reports and reference data are difficult to track because of the complexity of naming conventions for these substances, added to the fact that only a few laboratories currently have the analytical capabilities to test comprehensively for the many chemical and pharmacological classes represented. Due to the rapid rate of NPS turnover in the illicit drug marketplace, it is important that confirmed incidents of clinical or lethal intoxication are quickly reported and shared with the medical and forensic scientific communities. The focus of this review is on adverse events of intoxications with novel cannabinoids, stimulants, hallucinogens, benzodiazepines and opioids, as reported in emergency departments, death investigations, impaired driving cases and other forensic contexts published between January 2013 and December 2016. This review includes only cases that have been confirmed analytically.

Methods

Literature reviews were performed in PubMed (National Center for Biotechnology Information, US National Library of Medicine, Bethesda, MD, USA) for publications dated between January 2013 and December 2016. Search terms included specific names of NPS identified in laboratory casework and published literature, as well as general terms ("designer drugs," "novel psychoactive substances") and drug classes ("designer benzodiazepines," "novel hallucinogens," "synthetic cannabinoids"), which were cross referenced with outcome-based terms ("overdose," "intoxication," "death," "hospitalization"). In addition, government reports on websites discussing data for the years 2013–2016 were reviewed, including the National Forensic Laboratory Information System (NFLIS) (13) and the European Monitoring Centre from Drugs and Drug Addiction (EMCDDA) (14). Abstracts published by the Society of Forensic Toxicologists (15) and the American Academy of Forensic Sciences (16) from 2013 to 2016 were also reviewed.

Only reports that included analytical confirmation, either toxicological testing of the subject or on materials in the possession of the subject at the time of symptoms or events, have been included in the review. Cases with qualitative or quantitative toxicological identification were included in this review, irrespective of matrix (i.e., blood, serum/plasma, urine and tissue). Journal articles and published conference abstracts were fully reviewed with NPS identification and symptomatic information extracted, tabulated and organized by drug category. Structures were obtained from various in-print and online resources, including standard reference material manufacturer websites, SWGDRUG (17) and ChemSpider (18). All structures were verified by more than one source.

A series of tables (Tables III–VII) were constructed for novel cannabinoids, stimulants, hallucinogens, benzodiazepines and opioids, respectively. The tables are summarized by the NPS identified, including case history, clinical symptoms, autopsy findings and analytical results. Each report also includes the citation to the published case report.

Synthetic cannabinoids

Introduction

In late 2008, a botanist at US Customs and Border Patrol noticed a steady stream of "herbal incense" being express-shipped in USA (19). Routine testing did not reveal any illicit substances, but there were indications that drug users were getting high from smoking these products. Eventually HU-210, a synthetic cannabinoid originally synthesized in the late 1980s at Hebrew University, was identified as a substance sprayed onto dry plant material. Laboratory tests confirmed its presence in a shipment of herbal incense products and during the following years, the number and types of substances identified in these products continued to grow and evolve. Historically, these substances were synthesized by researchers, such as John W. Huffman (Clemson University), and pharmaceutical companies, as tools to investigate the cannabinoid receptor system and potential therapeutic agents. In recent years, the scientific manuscripts and patents published on the synthesis and potential activity of these cannabinoids provided a blue print to entrepreneurial chemists and drug users looking for legal alternatives to marijuana.

Chemistry

The chemistry of synthetic cannabinoids have been discussed in detail (7, 8, 20), and several websites provide tools to help identify synthetic cannabinoids based on their chemical structures (21, 22). In general, synthetic cannabinoids are chemically classified based on a structure consisting of core, linker, linked group and tail sections, as described in an EMCDDA report (21). The interactive tool on the associated website provides accurate information for the first several generations of compounds but still refers to the older terminology of

"ring" instead of "linked group." The newest generations of synthetic cannabinoids no longer have a ring in this section of the compound (21). The Cayman Chemicals Flipbook refers to the head, core and tail (22).

The naming convention of synthetic cannabinoids, like many NPS, is not consistent. Some compounds, such as JWH-018, AM-2201 or HU-210 are named based on the individual or institution where they were first synthesized. Newer compounds are often named based on an abbreviation of their chemical name or structural similarity to a previously named compound. The convention has been described elsewhere (8). As a result, there are often several names for the same compound. For example, *N*-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide is commonly called MAB-CHMINACA and ADB-CHMINACA. For this review the summary of previously published work will refer to the compound using the name in the publication with other common names provided, if applicable.

Pharmacology

Synthetic cannabinoids refer to the class of drugs targeting the endogenous cannabinoid (CB) receptors. The pharmacology of CB receptors and the pharmacology and toxicology of synthetic cannabinoids were recently reviewed (7). Stimulation of the central CB1 receptors produces the desired euphoria and relaxation effects sought by natural and synthetic cannabinoids users, while CB2 receptors, primarily located in the periphery, are critical for immune functions and represent a potential therapeutic opportunity.

Evaluation of synthetic cannabinoid activity is a multi-step process. Binding studies determine if the compound binds to the CB1 and/or CB2 receptors and *in vitro* functional assays provide preliminary evidence of receptor agonism. In general, *in vitro* assays evaluate the ability of a compound to illicit a chemical response from the receptor. Three different assays were reported in studies evaluating synthetic cannabinoids: (i) Guanosinetriphosphate (GTP) binding assay measuring G-protein-mediated release of guanosine diphosphate (GDP) and binding of GTP at the CB1 receptor, (ii) measurement of CB1 receptor mediated activation of G-protein regulated inwardly rectifying potassium channels (GIRKs) and (iii) cyclic adenosine monophosphate (cAMP) accumulation assays. All three assays compare an investigational compound and known CB1 receptor agonist, such as CP 55,490 or WIN 55,212.

Finally, *in vivo* functional assays, such as the mouse tetrad and drug discrimination studies compare the activity of new compounds to delta-9 tetrahydrocannabinol (THC), the primary pharmacologically active component of cannabis. These assays are appropriate for evaluating synthetic cannabinoid activity (7). Table I summarizes the receptor binding affinities and available data on *in vivo* and *in vitro* functional assays for synthetic cannabinoids associated with significant health effects.

In addition to CB1 and CB2 receptors, researchers investigated synthetic cannabinoids activity at other receptors. Wiley *et al.* (28) evaluated binding of first generation synthetic cannabinoids JWH-018, JWH-073, AM-2201, JWH-081, JWH-167, JWH-210 and JWH-391 to norepinephrine, serotonin, muscarinic, histamine, opioids, sigma, γ-aminobutyric acid A ($GABA_A$) and benzodiazepine receptors. All

Table I. Synthetic cannabinoids *in vitro* functional assays (cannabinoid receptor 1 (CB_1) inhibitory constant (k_i), drug concentrations that produce half-maximal (EC_{50}) and full (EC_{max}) response) and *in vivo* functional assays (spontaneous activity (SA), maximum antinociceptive effect (MPE), rectal temperature (RT) and ring immobility (RI))

Reference	Drug	CB_1 k_i (nM)[c]	*In vitro* functional assays[a]		*In vivo* functional assays (Mouse Tetrad Test)[b]			
			CB_1 EC_{50} (nM)	CB_1 EC_{max} (nM)	SA	MPE	RT	RI
Wiley (23)	CP55,940	0.59 (0.06)	23.3 (4.7)	124 (9)	–	–	–	–
	AB-CHMINACA	0.78 (0.11)	7.4 (1.5)	205 (14)	–	–	–	–
Banister (24)	WIN-55212-2	–	284	–	–	–	–	–
	THC	–	250	51 (3)	–	–	–	–
	PB-22	–	5.1	114 (3)	–	–	–	–
	5F-PB-22	–	2.8	108 (5)	–	–	–	–
Wiley (25)	CP55,940	1.00 (0.06)	25 (14.4)	–	–	–	–	–
	THC	67 (3)	–	–	15 (4.8–41.9)	12 (2.8–6.5)	4 (2.8–6.5)	3 (1.9–5.2)
	XLR-11	24 (4.6)	95 (20)	–	0.9 (0.36–1.64)	3.3 (2.22–4.77)	0.6 (0.58–0.91)	0.6 (0.57–0.64)
	UR-144	29 (0.9)	159 (38)	–	1.0 (0.55–2.25)	2.6 (1.83–4.05)	0.6 (0.51–0.74)	1.0 (0.64–1.66)
Hess (26)	CP55,490	1.28 (0.44)	–	100%[d]	–	–	–	–
	THC	3.87 (0.91)	–	60–70%	–	–	–	–
	5F-APINACA	1.94 (0.55)	–	120–125%	–	–	–	–
	NNE1	1.82 (0.35)	–	60–70%	–	–	–	–
Banister (27)	CP55,940	–	42	–	–	–	–	–
	THC	–	171	50 (11)	–	–	–	–
	5F-AMB	–	1.9	109 (3)	–	–	–	–
	MDMB-CHMICA	–	10	112 (2)	–	–	–	–

[a]*In vitro* functional assays: Publications by Wiley *et al.* (23, 25) employed GTP binding assays using CP55,940 as the normalization compound; Banister *et al.* (24, 27) used G-protein-gated inwardly rectifying K+ channels (GIRK) assays using WIN55212-2 or CP55,940 as the normalization compound; Hess *et al.* (26) employed cAMP accumulation assays using CP55,940 as the normalization compound.

[b]Mouse Tetrad Test: reported are either the ED50 (95% confidence interval) or percent inhibition of the level of activity (SA) or MPE achieved (dose in μg/kg). EC_{max} was 90% inhibition of SA, 100% MPE, –6°C change in rectal temperature and 60% RI. Dose is reported as μmol/kg.

[c]CB_1 k_i, CB_1 EC_{50} and CB_1 EC_{max} reported as mean (standard error of the mean).

[d]Hess *et al.* (26) reported functional activity of % of response compared to CP55,940.

tested compounds, with exception of JWH-210 and JWH-081, had low affinity (k_i = 185–4,815 nM) for the 5-HT_{2B} serotonin receptor and JWH-391 demonstrated affinity for the muscarinic M_1 receptor (k_i > 400 nM); no other significant binding was demonstrated. Binding activity at the serotonin receptor was evaluated with an *in vitro* functional assay. No agonist activity was identified. With exception of JWH-018, all compounds were weak antagonists of the serotonin $5HT_{2B}$ receptor.

Pharmacokinetics

Multiple recent reviews focused on the pharmacokinetics and metabolism of synthetic cannabinoids (7, 8, 29, 30). Presley *et al.* (8) published an exhaustive review on the analysis of biological matrices for synthetic cannabinoids, detection windows in those matrices, and data on their pharmacokinetics and metabolism. In general, metabolic pathways include hydroxylation along the tail, terminal carboxylation of the tail, and hydroxylation of the ring (head). Newer synthetic cannabinoids, such as ADB-CHMINACA, do not have a ring structure for the head and undergo hydroxylation of the terminal amide. Diao *et al.* (30) reviews the use of human liver microsome and hepatocyte incubations, rat administration studies and *in silico* prediction for identification of metabolic markers of synthetic cannabinoid intake in humans. In the absence of human administration studies the authors proposed performing human hepatocyte incubations paired with high-resolution mass spectral analysis and testing of authentic human urine samples to provide the best information on metabolite targets for manufacturers of standard reference material and laboratories developing routine tests.

Adverse effects

A wide range of adverse effects (Table II) have been associated with synthetic cannabinoid use including toxicity to multiple organ systems, gastrointestinal, cardiovascular, pulmonary and central nervous system effects (7, 29, 31–35). XLR-11 was specifically linked to acute kidney injury (AKI) (36–39). Trecki *et al.* (33) described outbreaks of synthetic cannabinoid exposure investigated by the Centers for Disease Control between August 2011 and April 2015. Outbreaks included AKI produced by XLR-11, agitated delirium associated with ADB-PINACA, and severe illness and death following exposure to MAB-CHMINACA (ADB-CHMINACA).

In 2014, Gurney *et al.* (7) reported one of the first extensive reviews of the literature on synthetic cannabinoid adverse effects. They documented a progression of reports from more anecdotal clinical reports with no toxicological or chemical confirmation in the early years of this trend (2008–2010), and documented the development of greater analytical capabilities in 2011 through 2013 where a more detailed clinical picture, larger series of cases, and increasing numbers of reports of toxicological confirmation often with quantitative results were included. Based on these reports from emergency rooms, poisons centers and psychiatric clinics, the adverse event picture was one predominantly of renal, pulmonary, gastrointestinal, psychiatric effects. The compounds in those early reports however were predominantly, naphthyl indole or benzyl indole compounds with their alkyl, and halo (usually fluoro) analogs. More concerning health threatening symptoms of seizures, psychosis and cardiovascular effects were, however, just beginning to appear. At that time, only three deaths had been reported in the medical literature linked to synthetic cannabinoids. Tait *et al.* (34) provides an extensive review which includes over 4,000 cases involving adverse events published in papers, letters and conference proceedings through December 2014. This review included cases of self-reported synthetic cannabinoid use and cases with analytical confirmation of exposure and concluded that synthetic cannabinoid intoxication includes more significant clinical effects than marijuana with tachycardia, agitation and nausea being the most commonly adverse effects. Subsequent review articles by Meyer *et al.* (29) and White (35) cover literature published in 2015 and 2016. The general conclusion of all authors who have reviewed the published literature is that synthetic cannabinoids demonstrate a higher risk of adverse effects and driving impairment than cannabis and unlike cannabis synthetic cannabinoids have been implicated in deaths.

Table II. Summary of toxicity profile of synthetic cannabinoid drug class

Organ system affected	Symptoms and signs
Central nervous system	Agitation, psychosis, irritability, seizures, sedation, coma, delirium, hallucinations, paranoia, anxiety, self-harm, psychomotor impairment
Cardiovascular	Tachycardia, hypertension, acute coronary syndrome, arrhythmia, chest pain, myocardial infarction
Pulmonary	Tachypnea, diffuse alveolar hemorrhages
Other	Nausea, vomiting, fevers, mydriasis, lack of convergence of gaze, acute kidney injury, hyperglycemia, hypokalemia, apoptotic cell death

Adapted from Alhadi *et al.* (40) and Gurney *et al.* (7).

Illness caused by AM-2201 was reported in 11 individuals who became ill after eating brownies prepared by a coworker (41). The onset of memory impairment, inappropriate giggling, light-headedness, numbness and tingling sensations of the face and mouth, dry mouth, blurred vision and sluggishness began within 1 h, and abated within 4 h. Although no biological sample analysis was performed, analysis of the brownies confirmed they contained AM-2201. A second case of oral exposure involved a 10-month-old infant who was taken to the emergency department after her mother found her found chewing on a "K2" cigarette (42). After arriving at the hospital, the child stopped responding to stimuli and had to be intubated. Serum analysis confirmed exposure to AB-PINACA; however, interpretation of AB-PINACA's role in the child's illness is complicated by the fact that the child also tested positive for influenza A.

Katz *et al.* (38) presented a series of 11 cases involving individuals who presented to a tertiary care medical facility during a 3-month period in 2015. Serum samples collected from the 11 individuals tested positive for MAB-CHMINACA (ADB-CHMINACA). The most common clinical findings were tachycardia (6/11) and agitation (4/11) and nine of the patients required intubation. One individual was found an estimated 24–36 h after using an herbal product and suffered anoxic brain injury leading to death. A cluster of AMB-FUBINACA (FUB-AMB) intoxications was reported in New York in July 2016 (43). A total of 33 people were exposed to an unknown drug and reported to have altered mental status described by bystanders as "zombie-like". Toxicology tested was reported for eight patients all of whom tested positive for a metabolite of AMB-FUBINACA.

Based on the lack of fatalities associated with THC overdose, medical examiners were initially hesitant to include exposure to synthetic cannabinoids as cause of death. Labay *et al.* (44) sought to investigate the role of synthetic cannabinoids as a cause or

contributor to death in 25 fatalities where synthetic cannabinoids were identified by blood analysis. Case history and pathology/toxicology findings were provided by the medical examiner who investigated each death. The information was compiled and sent to 11 medical examiners who agreed to participate by performing a secondary case review. They were asked to identify the role of synthetic cannabinoids in the case as "psychotic and/or excited delirium resulting in restraint followed by death," "behavior resulting in trauma or injury leading to death," "mixed drug intoxication including synthetic cannabinoids," "synthetic cannabinoid(s) only relevant drug class identified that contributed to death," "not clear if/how the presence of synthetic cannabinoid(s) contributed to death." Unanimity was only reached on two cases. In one case, all respondents concluded that synthetic cannabinoids were the sole toxicological agent responsible for death, and in the other case all respondents agreed that it was impossible to determine what role, if any, synthetic cannabinoids played in the death. There was consensus (>67% agreement) in most of the remaining cases as to whether to include the synthetic cannabinoid in the certification of death. Most cases where it was invoked included combined drug intoxication with alcohol and other drugs, and cases where an individual's behavior led to blunt trauma, respiratory arrest during police restraint or sudden death of unknown etiology. Despite the difficulty in determining the role of synthetic cannabinoids in death, in addition to these cases there are now multiple other case series on fatalities involving synthetic cannabinoids (45–52) in which 5F-PB-22, AB-CHMINACA, 5F-AMB, 5F-ADB, ADB-CHMINACA, MDMB-CHMICA and XLR-11 have been identified as the cause of death.

This increase in the number of fatalities in which synthetic cannabinoids have been invoked since the 2013 review by Gurney *et al.* (7) most likely reflects several factors: a greater appreciation among pathologists and medical examiners of the cardiovascular, seizure inducing and behavioral effects of the drugs; growing acceptance based on the growing body of literature of their potential role as a lethal agents; the availability of more comprehensive testing procedures by some laboratories to confirm the presence of the drugs; and the increasing potency of some of the most current synthetic cannabinoid drug classes, such as the indazole carboxamides (Table I). In addition to responsibility for illness and death, synthetic cannabinoids can impair driving (7). APINACA, 5F-APINACA, UR-144, XLR-11, AB-CHMINACA and AB-PINACA have all been identified as producing significant driving impairment (53–57). Individuals impaired by synthetic cannabinoids and examined by Drug Recognition Experts (DRE) typically have signs and symptoms consistent to person under the influence of cannabis. Chase *et al.* (57) comparing the effects of synthetic cannabinoids (n = 16) and cannabis (n = 25) in impaired drivers who completed a DRE examination protocol found that synthetic cannabinoids significantly increased frequency of confusion, disorientation, incoherence, slurred speech and horizontal gaze nystagmus (HGN) compared to cannabis.

The impact of UR-144 and its fluoro-pentanyl analog XLR-11 on driving was examined in 18 cases, 11 of which had DRE evaluations (54). The indicators observed in drivers with UR-144 and/XLR-11 in their blood were consistent with what is seen in cannabis impaired drivers and included lack of convergence, dilated pupils, heart rate and blood pressure elevated but within normal ranges, and body and eyelid tremors. In contrast to THC, HGN was present in half of the drivers in this study (53).

Peterson *et al.* (55) reported quantitative blood results on 58 drivers who tested positive for either AB-PINACA (n = 25) or AB-CHMINACA (n = 33) with concentration ranges of 0.6–41.3 ng/mL and 0.6–">10" ng/mL, respectively. Authors received case histories in 47 cases. Interaction with law enforcement was initiated for erratic driving (n = 15), being slumped over or unconscious (n = 13), inappropriate stopping in roadway (n = 5), collisions with stationary objects (n = 11) or calls to EMS (n = 2). The results of DRE exams were also reported for 20 individuals. HGN was observed in 50% of AB-CHMINACA and 60% of AB-PINACA cases with the likelihood of HGN being observed decreasing as concentrations of the drugs increased.

A summary of case information for fatalities, impaired driving and illnesses are summarized in Table III.

Discussion

These case reports and series provide information on the morbidity and mortality associated with synthetic cannabinoids but care must be taken when interpreting their role in illness and death. Thousands of compounds have been synthesized by various research groups, and now illicit laboratories, but only a small fraction have been demonstrated to bind to or to have activity at the CB1 receptor. In some cases, structural analogs appeared in herbal incense products, which later were subsequently shown to be inactive. For example, in 2014, Uchiyama *et al.* (58) reported identifying FUBMINA, the AM-2201 benzimidazole analog, in street products but research published by Wiley *et al.* (59) later showed that FUBIMINA had low affinity for the CB1 receptor, required high concentrations to stimulate GTP binding and did not display cannabinoid-like effects in the mouse tetrad study. This highlights the importance of the data presented in Table I. The combination of binding studies, *in vitro* assays, *in vivo* assays and published case reports provides a basis for interpretation of synthetic cannabinoid results in clinical, post-mortem and driving cases.

Multiple reports of delirium along with increases rates of tachycardia and elevated blood pressure following synthetic cannabinoid exposure raise the question of the potential role of synthetic cannabinoids in cases of excited delirium (33, 60, 61). Therefore, testing for synthetic cannabinoids should be considered under circumstances of agitation, delirium and dissociation, often accompanied by hyperthermia, disrobing and violent outbursts, especially in the context of restraint and in custody police deaths. In post-mortem cases, the mechanism of toxicity for synthetic cannabinoids is unclear. In several cases, individuals were deceased upon discovery with no witnesses to death (38, 46–51). In the cases of witnessed collapse or medical care, symptoms indicative of cardiac or neurological toxicity, such as gasping for air, sudden collapse and seizures, were reported (45, 52). This is consistent with the reported adverse effects of individuals who were hospitalized for synthetic cannabinoid intoxications. It is worth noting that the cases, where synthetic cannabinoids were implicated in death, did not typically involve other drugs. While the mechanisms of toxicity are not well understood, the increasing binding affinity of the latest drugs raises the possibility of greater potency, with a corresponding increase in the risk of serious adverse events. Given the rapid turnover of these substances in the drug supply available to users, it is critical that laboratories frequently update the scope of their testing, and that investigators consider the potential role of synthetic cannabinoids in impaired driving and post-mortem cases.

Table III. Synthetic cannabinoids case histories with clinical symptoms, autopsy findings and primary drug and additional drug concentrations

Drug	History	Clinical symptoms/autopsy findings	Drug results (ng/mL unless specified)	References
5F-ADB	34 y/o M found dead at home holding a homemade foil pipe and with herbal blends packages.	No significant injuries; postmortem lines of blood noted on chest, arms, abdomen and front of thighs; airway completely occluded by stomach contents and lungs markedly congested. Asphyxia cause of death following synthetic cannabinoid use.	Stomach contents: 3.2 tissue: <0.5–8.0 ng/g +MAB-CHMINCA: Blood 6.1–10.6; pericardial fluid 14.9; gastric contents 10.6; tissue 9.8–156 ng/g 5F-ADB unstable in biological specimens.	(47, 48)
5F-AMB	34 y/o M found dead at home with "Apollo" herbal incense in pocket.	No remarkable autopsy findings and no significant medical hx. Cause of death synthetic cannabinoid toxicity.	Subclavian blood: 0.3	(50)
5F-PB-22	17 y/o M used alcohol and synthetic cannabinoids over a day. Early morning next day gasping for air prior to collapsing. Transported to hospital and pronounced dead.	No significant injury or natural disease. Cause of death 5F-PB-22.	Femoral blood: 1.1 +Blood ethanol 33 mg/dL	(45)
	22 y/o M to ED[a] "ill and diaphoretic." Admitted to hospital and diagnosed with acute liver and kidney injury; coagulopathy, acute respiratory failure, hypoxia, severe anion gap metabolic and lactic acidosis, multi-symptom failure and death.	Cause of death fulminant liver failure with THC and 5F-PB-22.	Serum (~7 h before death): 1.1	(45)
	19 y/o M pronounced dead at home day after party with friends. Drinking alcoholic beverages and smoking herbal incense.	Bilateral pulmonary, spleen, liver and kidneys congestion. Cause of death synthetic cannabinoid use.	Iliac blood: 1.5	(45)
	19 y/o M unconscious at party, returned home next day, felt light-headed, dead the next morning.	Bilateral pulmonary edema, viscera congestion, necrotizing granulomatous inflammation. Cause of death suspected acute 5F-PB-22 drug intoxication.	Superior vena cava blood: 1.5	(45)
AB-CHMINACA	30 y/o M found dead in car with lighter in hand and open package of "Herbal Incense The Super Lemon".	No significant findings or obvious cause of death. Diphenidine implicated in death.	Tissue: 7.6–38.9 ng/g +Adipose tissue: 18.7 ng/g 5F-AMB; Diphenidine blood 707–923; urine: 376; tissue: 1,300–11,100 ng/g	(46)
	10 Drivers with one or more of the following driving behaviors: erratic driving, unconscious in vehicle, inappropriate stopping, collisions with stationary objects.	HGN[b] (5), VGN[c] (4), LOC[d] (3), Pulse >90 bpm (4), BP[e] < 120/70 mmHg (7), eyelid tremors (1) Walk-and-Turn ($n = 9$): 1 clue (3), 2 clues (1); 4 clues (3); 7 clues (1). OLS[f] ($n = 9$): 1 clue (2); 2 clues (1); 3 clues (2); 4 clues (2).	Blood: 1.0–9.5	(55)
AB-PINACA	10 Drivers with one or more of the following driving behaviors: erratic driving, unconscious in vehicle, inappropriate stopping, collisions with stationary objects.	HGN (6), VGN (2), LOC (7), Pulse >90 bpm (1), BP < 120/70 mmHg (7), eyelid tremors (2). Walk-and-Turn ($n = 9$): 1 clue (2), 2 clues (2); 3 clues (1); ≥5 clues (4). OLS ($n = 9$): 1 clue (1); 2 clues (4); 3 clues (1); 4 clues (1).	Blood: 2.6–>10	(55)
AMB-FUBINACA (FUB-AMB)	18 M patients (25–59 y/o) transported to hospital after exposure to unknown drug. Toxicology results reported for eight patients. Index patient: 28 y/o M.	Index Patient: "Blank stare", lethargic, sweating, overall GCS[g] 13, eye response score 4, motor response score 5. Behavior normalized after ~9 h.	Blood ($n = 1$): 68 Serum ($n = 8$): AMB-FUBINACA acid metabolite 77–636 +Urine ($n = 3$): AMB-FUBINACA acid metabolite < 15–165	(43)
MAB-CHMINACA (ADB-CHMINACA)	18 y/o M unresponsive in parking lot.	Tachycardic, sluggish pupils.	+Serum +Urine caffeine	(38)
	28 y/o M hx[h] of substance abuse.	Unresponsive, hallucinating, tachycardic. Required intubation.	+Serum	(38)

			+Urine Caffeine, morphine, midazolam, lorazepam	
	17 y/o F with no medical hx.	Agitated, delirious, tachycardic. Treated with benzodiazepines.	+Serum +Urine Lorazepam	(38)
	14 y/o M with no medical hx found unresponsive in street.	Agitated, combative, required intubation.	+Serum +Urine Norfentanyl	(38)
	13 y/o F with hx of marijuana abuse.	Intermittently unresponsive and combative, sluggish pupils, tachycardic, required intubation.	+Serum +Urine Phenylephrine, midazolam, fentanyl, norfentanyl, diphenhydramine, cotinine	(38)
	13 y/o M with no medical hx found unresponsive in park.	Periods of agitation and combative, required intubation.	+Serum +Urine Lorazepam, hydroxymidazolam	(38)
	50 y/o M with hx of polysubstance abuse found unresponsive.	Apneic and cyanotic, required intubation.	+Serum +Urine ethanol, naloxone, metoprolol, caffeine	(38)
	50 y/o F with hx of bipolar disorder witnessed having seizures.	Tachycardic, required intubation.	+Serum +Urine acetaminophen	(38)
	19 y/o F with hx of epilepsy, bipolar disorder and substance abuse suffered seizure.	Sinus arrhythmia with non-specific T-wave abnormality, required intubation.	+Serum +Urine morphine, norfentanyl, cocaine, amphetamine, methamphetamine, codeine, midazolam, lorazepam	(38)
	14 y/o M with hx of substance abuse found agitated.	Bradycardic, periods of unresponsiveness and combativeness, required intubation.	+Serum +Urine Sertraline	(38)
	20 y/o M with no medical hx found unresponsive. Estimated without medical care for 24–36 h.	Hypothermic, tachycardic, required intubation. Significant rhabdomyolysis, acute renal failure and anoxic brain injury. Life support withdrawn.	+Serum +Urine Sertraline	(38)
MDMB-CHMICA	22 y/o M unresponsive ~15 min after smoking brown powder. Asystole when ambulance arrived. Circulation restored but patient declared brain dead following day.	No significant medical hx and autopsy revealed no signs of injury or illness to explain death. Cause of death MDMB-CHMICA overdose.	Antemortem serum (~2 h after collapse):1.4 Post-mortem spleen blood: 0.1α +Serum: 5.3 Mirtazapine; 1.5 THC	(52)
NNE1	Early 20s y/o M found dead in room. Dried herbal product named "Fairy Evolution" and smoking paraphernalia found in room.	Poor appetite and weight loss in 10 months prior to death. No external injuries. Significant lung congestion. Cause of death acute circulatory disturbance induced by NNE1.	Serum: 0.77–0.92 Blood: 0.64–0.99 Brain: 0.76 ng/g Heart: 0.82 ng/g Lung: 1.06 mg/g Liver: 1.31 ng/g Kidney: 0.92 ng/g Adipose tissue: 42.9 ng/g	(49)
UR-144	6 Drivers: inability to maintain lane, inconsistent speed, inappropriate stopping, driving on curb.	Poor coordination (6), bloodshot eyes (6), watery eyes (4), dilated pupils (2), droopy eyelids (1), slurred speech (5), HGN (2), LOC (3), Tremors (5). Walk-and-Turn ($n = 5$): 2 clues (2); 3 clues (2); 5 clues (1). OLS (n = 7): 1 clue (2); 2 clues (2); 3 clues (1). FTN ($n = 4$): normal. Internal clock ($n = 4$): 11–40 s.	Blood: qualitative	(54)
	19 y/o M; single car crash	Hyperactive, pale skin, wide sluggish pupils; HR[i] 90 bpm; staggering gait.	Blood: 14.6	(56)

Table continues

Table III. Continued

Drug	History	Clinical symptoms/autopsy findings	Drug results (ng/mL unless specified)	References
XLR-11	29 y/o F found dead at home. Last seen alive day before by boyfriend who reported she was agitated and intoxicated. Packages of "Black Dragon" found at scene.	No signs of natural disease. Cause of death certified as synthetic cannabinoid toxicity.	Blood: 1.4 +Blood diphenhydramine 81	(51)
	32 y/o F with hx of drug abuse presented to ED with chest pain, nausea and agitation. Diagnosed with anxiety and released. Later same day, found unresponsive on floor at friend's house and taken to hospital where pronounced dead.	Significant pulmonary edema and congestion, acute visceral congestion and mild pulmonary anthracosis observed on autopsy. Cause and manner of death undetermined.	Blood: 0.61	(51)
	22 y/o M driving cargo van collided with vehicle stopped in traffic. Witness indicated driver was "really high on weed."	DRE exam indicated slow/mumbled speech, lethargy, rigid muscle tone, incoordination, no HGN, LOC in one eye, poor performance on Walk-and-Turn and OLS.	Blood: 1.3	(53)
	Eight drivers with one or more of the following driving behaviors: inability to maintain lane, inconsistent speed, inappropriate stopping, driving on curb.	Poor coordination (4), bloodshot eyes (7), watery eyes (3), dilated pupils (4), droopy eyelids (2), slurred speech (5), HGN (4), LOC (5), Tremors (4). Walk-and-Turn (n = 7): 1 clue (2), 2 clues (2); 3 clues (1); 4 clues (2). OLS (n = 7): 1 clue (4); 2 clues (2); 3 clues (1). FTN (n = 4): 2 clues (1), 3 clues (1), 5 clues (2). Internal clock (n = 5): 21–44 s.	Blood: Qualitative	(33)
XLR-11 and UR-144	Four drivers with one or more of the following driving behaviors: inability to maintain lane, inconsistent speed, inappropriate stopping, driving on curb.	Poor coordination (2), bloodshot eyes (3), watery eyes (2), dilated pupils (1), slurred speech (2), HGN (3), LOC (2), Tremors (3). Walk-and-Turn (n = 4): 2 clues (1); 5 clues (1). OLS (n = 4): 1 clue (1); 2 clues (2). FTN (n = 3): 3 clues (1), 5 clues (1). Internal clock (n = 3): 25–45 s.	Blood qualitative for XLR-11 and UR-144	(33)

[a]Emergency department.
[b]Horizontal gaze nystagmus.
[c]Vertical gaze nystagmus.
[d]Lack of convergence.
[e]Blood pressure.
[f]One leg stand.
[g]Glasgow coma scale.
[h]History.
[i]Heart rate.

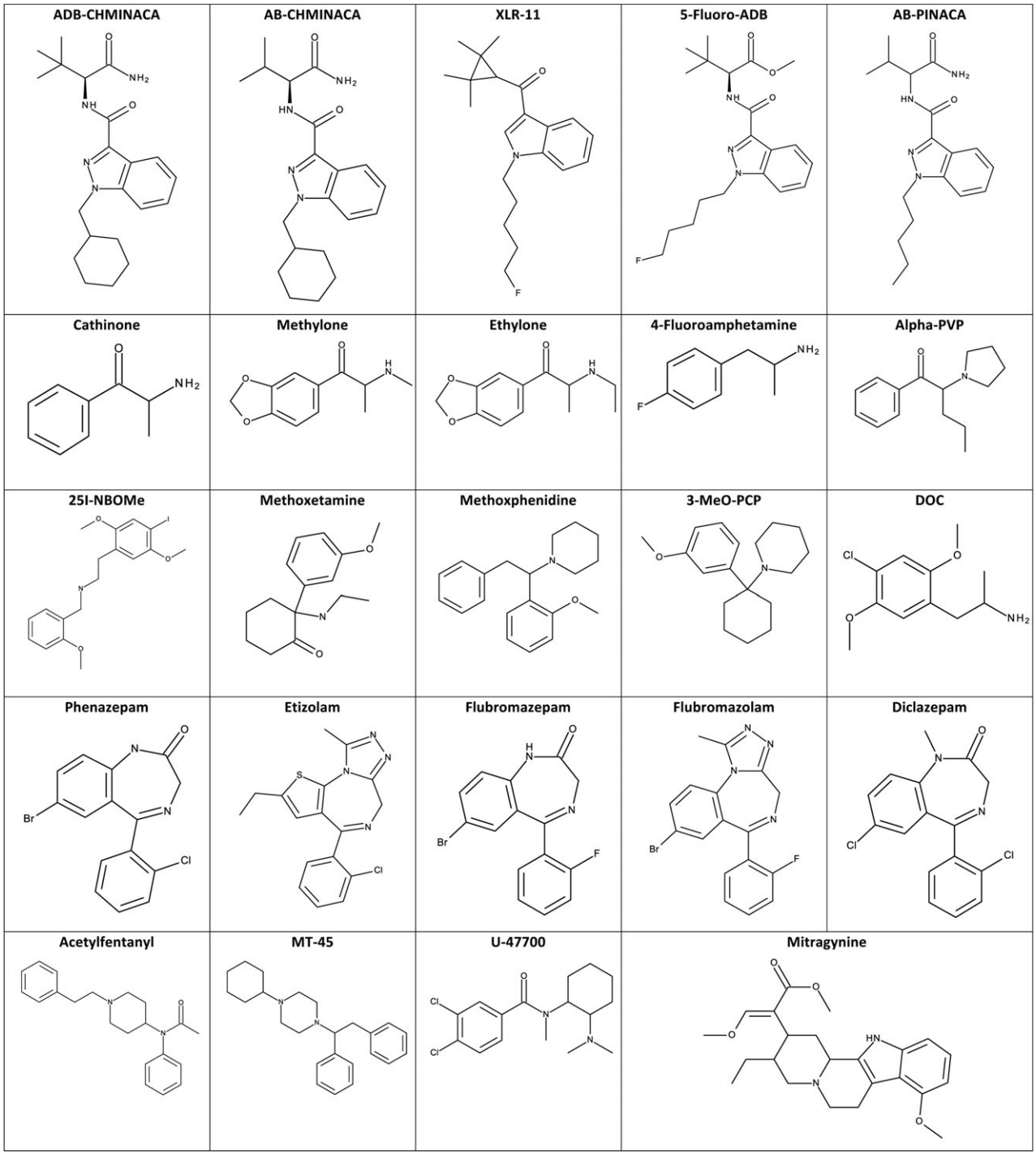

Figure 1. Structures of novel psychoactive substances.

Synthetic stimulants

Introduction

The synthetic stimulant drug class consists of amphetamines, phenethylamines and cathinones. Synthetic cathinones are derived from cathinone (Figure 1), a monoamine alkaloid present in the plant *Catha edulis* (Khat). The methylated analog of cathinone, methcathinone, was first synthesized in 1929, with reports of abuse as early as the 1990s (62). Subsequently, 4-methylmethcathinone (mephedrone) and beta-keto amphetamines, such as methylenedioxypyrovalerone (MDPV), which retained the methylenedioxy bridge were reported as emerging analytes of abuse in the early 2000s in the UK and Europe (62). Adverse effects included increased heart rate and blood pressure, motor excitation and euphoria. The empathetic and emotional effects (feelings of closeness, identification, compassion), enhanced responsiveness to touch (entactogenicity) and amplification of other intimate and sensory-based responses led to their popularity in recreational settings including raves, dance music clubs and festivals. By

the late 2000s, novel compounds including methylone and alpha-pyrrolidinopentiophenone (alpha-PVP) increased in prevalence. Alpha-PVP in the Europe became highly popular in 2013 (63). The use of these analogs continued to proliferate in concordance with the Drug Enforcement Agency's (DEA) scheduling actions. In 2009, only five synthetic cathinones were reported to the NFLIS; however, in 2015, 35 new cathinones were reported, with methylone, alpha-PVP and ethylone being the most prevalent (64). In the US, methylone, alpha-PVP and ethylone (as a positional isomer of butylone) are all now Schedule I substances (65).

Pharmacology

Mechanisms of action for synthetic cathinones involve interactions with dopamine, serotonin and norepinephrine transporters with varying affinities and selectivities, as shown in *in vitro* studies, including human cell lines and preclinical models (66–70). Ring-substituted cathinones, such as methylone, act as transporter substrates that increase the release of dopamine, serotonin and norepinephrine. The presence of a pyrrolidine ring, as in alpha-PVP, act as transport blockers (reuptake inhibitors) at the dopamine transporter (67–70). Increasing the length of the alpha-carbon chain increased affinity and potency at the dopamine transporter (69). Compounds with a higher potency at the dopamine transporter, including alpha-pyrrolidinophenones and 4-fluoroamphetamine (4-FA), exhibit stimulant properties similar to methamphetamine (69), while cathinones that have similar potencies at dopamine and serotonin transporters, or higher potency at the serotonin transporter may have more empathogenic activity (i.e., ethylone) (70).

The onset of synthetic cathinone effects occur within 30–45 min of administration, with desired effects lasting from 1 to 3 h, and undesirable effects lasting for days (71). Reported synthetic cathinone effects include increased energy, alertness, concentration and euphoria; effects are similar to those of amphetamine and cocaine (62, 66, 72, 73). Adverse physiological effects include cerebral edema, diaphoresis, hyperreflexia, hypertension, hyperthermia, dilated pupils, tachycardia, myocardial infarction, seizures, bruxism, nausea and vomiting. Prominent adverse neuropsychiatric effects include agitation, aggression, hallucinations, paranoia, psychosis and serotonin syndrome. Hallmark indicators of toxicity and overdose include hyperthermia, diaphoresis, tachycardia, agitation and hypertension (72). Psychosis may be pronounced, with patients experiencing paranoia, hallucinations (primarily visual) and delusions. Toxic sequelae can include liver and kidney failure, rhabdomyolysis and development of compartment syndrome (increased pressure in a muscle compartment) that can lead to muscle and nerve damage and problems with blood flow, and ultimately death (62, 72). Excited delirium syndrome has been cited as a contributing factor in fatal cases involving highly agitated persons held in police custody, restrained or incapacitated by electrical devices in cases without an anatomical cause of death (74). Table IV includes synthetic stimulant driving impairment cases, fatalities and illnesses.

Methylone

Methylone (Figure 1) intake has been associated with adverse events and deaths including accidental drownings, sudden cardiac death, suicides, acute methylone intoxication and polydrug intoxications (11, 75–77, 88, 89). Additionally, methylone was detected in 13% of urine cases ($n = 45$) received from victims of sexual assault cases in 2013 in Miami-Dade (90). In a 3-year review by the New York City, Office of the Chief Medical Examiner, "bath salts" (primarily methylone) contributed to the cause of death in 50% (15 of 30) of cases (89). The remaining 50% of cases had methylone quantitated, but were not contributory to the cause of death. Three postmortem cases with available case histories have been reported, however limited information regarding the specific symptoms or onset of effects exist as these events were unwitnessed. Elliot and Evans (11) reported post-mortem blood methylone concentrations of 100, 4,310 and 11,000 ng/mL. Of the six post-mortem cases discussed here, the range for methylone concentrations in blood is from 70 to 11,900 ng/mL.

Methylone is primarily metabolized via the Cytochrome P450 2D6 enzyme (91). Primary metabolites identified included demethylenation, 3,4-dihydroxy-*N*-methylcathinone (HHMC), 4-hydroxy-3-methoxy-*N*-methylcathinone (HMMC) and 3,4-methylenedioxycathinone (MDC) and 3-hydroxy-4-methoxymethcathinone that is subsequently conjugated (91, 92). In authentic urine specimens, the parent drug was more abundant than the metabolites; however, identified metabolites included the keto-reduced and *n*-dealkylated products (93).

Ethylone

The *n*-ethyl derivative of methylone, ethylone (Figure 1), was implicated in a series of postmortem cases ranging from gunshot wounds, blunt force trauma and fatal intoxications (78, 94). In nine postmortem cases, ethylone blood concentrations ranged from 38 to 2,572 ng/mL with one case below the 25 ng/mL limit of quantification. The case history was provided in only one fatality, and involved the subject reportedly ingesting pills and using illicit substances before falling asleep and being found dead the following morning. Clinical symptoms were not reported. The autopsy reported congestion and edema in the lungs, a muscular and enlarged heart (although this may be attributed to subject taking human growth hormone) and urinary retention (78). There was no other evidence of disease or trauma. The drug was found in multiple specimens, allowing for calculation of ratios, notably, the central to peripheral blood ratio was 0.97.

4-Fluoroamphetamine

4-FA (4-FMP; PAL-303; "Flux") (Figure 1), also known as para-fluoroamphetamine (PFA), is an emerging synthetic stimulant recently implicated in four cases that resulted in emergency department visits and two driving under the influence of drugs (DUID) case (79, 80, 82, 95). Subjects presenting to the emergency department showed signs of hyperkinesis, tachycardia, elevated heart rate and temperature (79, 80, 95). In the DUID cases, one subject was stopped as part of routine traffic control, while the other subject was involved in crash that resulted from the subject straying off the road and overturning the vehicle. In both cases observed effects were consistent with those of other CNS stimulants including dilated pupils and elevated vital signs (82).

Alpha-PVP

Overall, 18 DUID and 3 fatalities involving alpha-PVP (Figure 1) were reported between 2012 and 2015 (96). In the three postmortem cases, blood concentrations ranged from 30 to >20,000 ng/mL. In the DUID investigations, blood alpha-PVP ranged from <5 to 90 ng/mL, with driver behavior ranging from incoordination, to unresponsive and passing out. Physical presentations included glassy, bloodshot eyes with constricted pupils and slurred speech. Over 4 years in the Swedish STRIDA project, there were 42 intoxications where alpha-PVP was the only NPS stimulant detected (97). The median (range) serum alpha-PVP concentration was 64 (4–606) ng/mL and urine ($n = 25$) alpha-PVP was 1,782 (2–41, 294) in DUID cases (96). In postmortem cases

Table IV. Synthetic stimulants case histories with clinical symptoms, autopsy findings and primary drug and additional drug concentrations

Drug	History	Clinical symptoms/autopsy findings	Drug results (ng/mL unless specified)	References
Methylone	19 y/o M collapsed outside in warm weather (70°F) while jogging <2 miles. He was unresponsive, pulseless and apneic. Past hx[a] was significant for two previous motor vehicle crashes in 2 mo.[b] with only minor injuries.	External examination revealed several fractures and abrasions, but no cranial or cervical spine fractures. Pulmonary congestion and edema, mild peribronchial inflammation and mild hepatic portal and lobular inflammation.	Blood: 70	(75)
	19 y/o F with hx of recreational drug use found floating face down about 100 yards from shore. On the night of her death, wave conditions were 2–3 feet and water temperature 55°F. She spoke with a friend that evening and stated she was going to "get in the water."	Autopsy findings consistent with drowning, including frothy fluid in airway, pulmonary congestion/ edema and maceration of her palms and soles. Abrasions and contusions consistent with being tossed in surf.	Peripheral blood: 3,400 Central blood: 3,400 Vitreous: 4,300 Liver: 11 mg/kg Gastric contents: 1.7 mg	(76)
	58 y/o M found nude on his bedroom floor. Large amounts of blood found on body and throughout residence. 12 h prior to finding body, decedent stated he would not be attending a holiday party due to not feeling well.	At autopsy, minor blunt force injuries noted to head, neck, truck and extremities, laceration on right supraorbital ridge. Autopsy findings remarkable for hypertensive and atherosclerotic cardiovascular disease with cardiomegaly and atherosclerotic coronary artery disease.	Femoral blood: 11,900 Heart blood: 15,300 Urine: 1,600,000 Vitreous: 21,900 Liver: positive Bile: 318,000 Gastric contents: 65 mg/150 mL +urine butylone	(77)
Ethylone	30 y/o M reportedly ingested pills and other illicit drugs with female friend. Both fell asleep and when she woke the following afternoon he was dead.	Congestion and edema noted in lungs, with urinary retention. Heart was large and muscular, but he also used human growth hormone. No evidence of disease or trauma and no family hx of cardiovascular disease.	Peripheral blood: 390 Central blood: 380 Liver: 1.4 mg/kg Vitreous: 580 Urine: 20,000 +Peripheral blood morphine 50; THCCOOH 3.6; alprazolam <50; THC < 1, naproxen < 5,000	(78)
4-FA	18 y/o M presented to ED[c] with vomiting, shortness of breath, chest tightness and altered mental status about 5 h after using new and unfamiliar street drug.	Initially subject was alert, oriented, diaphoretic, with normal respiratory rate of 16/min, HR[d] 103 bpm[e] and BP[f] of 130/52 mmHg. An echocardiogram showed sinus tachycardia. Subject's condition declined. 5 h after arriving, developed cardiogenic shock requiring intra-aortic balloon pump, inotropic and ventilatory support. Pulmonary edema. Echocardiogram showed ventricular hypokinesia.	Serum: 118 Urine: 64,000 +serum: naproxen, trazodone and cotinine +urine: naproxen, fluoxetine, trazodone, naltrexone, nicotine and cotinine	(79)
	18 y/o F presented to ED after drinking two capfuls of "Molly's Mosquito cap" with headache, vomiting, light-headedness and diaphoresis.	On admission, complained of anxiety. An echocardiogram 36 h after ingestion showed a cardiac ejection fraction of 10–15% with mild left ventricular dilation and severe hypokinesis. 48 h after admission, subject remained slightly tachycardia although symptoms improved.	Urine: 37,000	(80)
	27 y/o M with polysubstance dependence presented to ED after found agitated and lying in street.	HR 156 bpm and rectal temperature 106.5°F. Diaphoresis, dilated pupils, hyperreflexia without clonus and non-sensible speech.	Serum 23 h post-admission: 1,400 Urine 4 h post-admission: 285,000 Urine 23 h post-admission: 124,000	(81)

Table continues

Table IV. Continued

Drug	History	Clinical symptoms/autopsy findings	Drug results (ng/mL unless specified)	References
			+serum: PCP 4.7, diazepam 170, nordiazepam 83 +urine 4 h post-admission PCP 107 +urine 23 h post-admission, PCP 12, diazepam 420, nordiazepam 2,000	
	35 y/o M stopped by police for routine traffic control. Police found marijuana and several herb mixtures only labeled with chemical formulas. Subject admitted smoking joint the day prior.	Police noted slow coordination, deficiency in concentration, washed-out pronunciation, agitation, restlessness, dry mouth, eyes reddened and glassy, delayed reaction time and enlarged pupils. Orders had to be repeated multiple times and he could not follow long sentences.	Serum 1 h and 55 min after incident: 90+serum: THC 0.9, THCCOOH 6.8, 11-OH THC < 0.8	(82)
	Police responded to traffic crash. Appeared car left road and turned over. 41 y/o F driver stated crash occurred because of micro-sleep (short sleep periods of secs when subject is unresponsive)	No police observations reported. During blood collection, physician noted subject appeared impaired and stated she had injected a bath salt 2 days prior.	Serum 2 and 25 after crash: 89.9 +serum: 2-diphenyl-methylpiperidine (2-DPMP)356, MDPV 21.3, benzedrone (<10)	(82)
Alpha-PVP	Mid-20s y/o M suddenly became violent and he was restrained. He collapsed after 2 h of struggling. 30 min resuscitation efforts were unsuccessful.	Facial congestion and nail cyanosis were severe. Petechiae found in conjunctivae, oral mucosa, submental and upper neck. Injuries noted due to restraints. Heart showed concentric hypertrophy without coronary sclerosis. Other organs, including lungs, showed severe congestion. Histology revealed diffuse and severe myocardial contraction bands.	Serum: 411	(83)
	44 y/o M with recreational drug abuse hx injected a powder named "Smokin' Slurry Scrubba." He acted irrationally, stripped off his clothes, jumped a barbed-wire fence and smashed a window. He was apprehended and restrained by security where he suffered cardiac arrest estimated to have lasted for 16 min.	On arrival to ED, subject was hypertensive with 39.9°C temperature. He had dilated pupils unreactive to light. Hyperkalemia, rhabdomyolysis, ischemic hepatitis, elevated lactate and acute renal failure. 43 h after cardiac arrest, subject declared brain dead and removed from supportive care. At autopsy, cerebellar tonsillar herniation and pulmonary edema noted.	Blood: Alpha-PVP qualitatively determined in antemortem and postmortem blood. No other drugs detected.	(84)
	28 y/o M with hx of designer drug abuse transported to ED in asystole and died 30 min later, despite resuscitation efforts. White powder labeled "α-PVP" and material data safety sheets for alpha-PVP and pentedrone recovered.	At autopsy, pulmonary edema and moderately advanced atherosclerotic lesions. Microscopic examination of heart revealed chronic changes and presence of heart failure cells.	Blood: 901, 185 OH-α-PVP Liver: 2,610 ng/g, 2,264 ng/g OH-α-PVP Kidney: 463 ng/g, 294 ng/g OH-α-PVP Brain: 120 ng/g, 91 ng/g OH-α-PVP Stomach Contents: 4,091 ng/g, OH-α-PVP 47 ng/g +blood, pentedrone 8,794; +liver, pentedrone 100,044 ng/g +kidney, pentedrone 22,102 ng/g +brain, pentedrone 13,248 ng/g +stomach contents, pentedrone 500,534 ng/g	(85)

	32 y/o M with no prior drug use hx experienced syncope 30 min after ingesting "NRG-3." He felt ill, had difficulty breathing and lost consciousness. CPR was unsuccessful.	Autopsy showed moderate obesity, pulmonary edema, atherosclerotic heart disease and fatty liver fibrosis.	Plasma: 1,500 Urine: >5,000 +plasma, THC 3.3, THCCOOH 14.2, 11-OH-THC 2, alcohol 3.65 g/L +urine, THCCOOH	(86)
	21 y/o M admitted to ED with tachycardia after ingesting "NRG-3."	On admission, HR 128 bpm, BP 160/90 mmHg, 30 breaths/min and a 37.1°C temperature. Mydriasis present in both eyes and initial lab results showed rhabdomyolysis without renal failure. Subject experienced hallucinations 12 h after last reported intake.	Plasma: 235 Urine: >5,000 +urine, THCCOOH	(86)
Alpha-PVP, methylone and ethylone	34 y/o M stopped for improper lane travel and stopping prior to stop sign. Driver entered oncoming lane of travel and crossed center line three times in 1.5 miles.	Driver appeared disoriented and confused and with slurred speech, bloodshot watery eyes and difficulty dividing his attention. During DRE[g] evaluation, 2 of 6 clues on HGN[h], 7 of 8 on walk and turn, and 4 of 4 on OLS[i]. During Romberg balance, subject had extreme eyelid tremors, swayed with inability to stand still. DRE also noted agitation during evaluation. HR 90, 106 and 80 bpm, elevated systolic BP 150/82 mmHg and temperature 98.6°F.	Blood: alpha-PVP 63, methylone 6.1, ethylone	(87)

[a]History.
[b]Months.
[c]Emergency department.
[d]Heart rate.
[e]Beats per minute.
[f]Blood pressure.
[g]Drug recognition expert.
[h]Horizontal gaze nystagmus.
[i]One leg stand.

where subjects required restraint, two died from sudden cardiac deaths (83–85).

Metabolic products of alpha-PVP were determined in rat and human specimens, with reduction of the ketone to an alcohol (5-OH-α-PVP; diasteromers), hydroxylation at the alkyl chain (OH-alkyl-PVP) and on the phenyl ring (OH-phenyl-PVP), oxidation of pyrrolidine ring to a lactam (2″-oxo-PVP) and a carboxylic acid (carboxyamino-PVP), and degradation of the pyrrolidine ring to a primary amine (amino-PVP) (93, 98–101). In recreational users, one of was identified as the primary blood metabolite; urinary metabolites included, one the 5-OH-α-PVP diasteromers, 2″-oxo-PVP and butylamino-OH-PVP (102).

Mixed drug cases

In one DUID case, a male subject was stopped for improper lane travel, after crossing into the oncoming lane of traffic, and stopping several feet short of a stop sign (87). The officer noted that the driver was confused and disoriented, with slurred speech and watery bloodshot eyes. The alcohol breath test was negative, leading to a DRE evaluation. The alpha-PVP blood concentration was 63 ng/mL, methylone 6.1 ng/mL, and the sample was additionally positive for ethylone but was not quantitated. In another case, a 46-year old male was brought to the Emergency Room after ingesting a large quantity of zolpidem with suicidal intent (103). The man admitted to continuous recreational drug intake for the prior 3 months that had led to delusions and paranoia. A white powder recovered from the subject's home contained MDPV, mephedrone, butylone and alpha-PVP. The subject's urine was positive for MDPV.

In one reported case, the postmortem pentylone concentration was 340 ng/mL and for butylone, 550 and 4,420 ng/mL (11).

Discussion

The excitatory nature of synthetic stimulants and their effects on the sympathomimetic systems are likely to continue to result in toxicity and deaths in susceptible individuals, especially those with cardiac compromise. General symptoms associated with synthetic stimulant use produce effects including elevated heart rate, increased blood pressure and dilated pupils. With respect to impairment, individuals under the influence of these substances often exhibit hallucinations, paranoia, anxiety and/or aggression with risk of excited delirium and life-threatening cardiovascular effects (100). Several of the postmortem cases have limited information regarding onset of effects and clinical symptoms as many of the deaths are unwitnessed. In those cases, scene investigation is critical as recovered paraphernalia may provide evidence as to what substance may be implicated in the death.

There continues to be some turnover in the synthetic stimulant drug markets and the disappearance of drugs like alpha-PVP following scheduling actions means that the range of drugs available to users will continue to evolve. The appearance in recent casework and seized drugs of *N*-ethyl pentylone and dibutylone suggests that although slower than the activity in the synthetic cannabinoid market, laboratories will need to continue to be vigilant for the appearance of synthetic stimulants.

Continued emergence of novel synthetic stimulant compounds is expected. Currently few published reports are available for pentylone, butylone, *N*-ethyl pentylone and dimethylone, although they are now being encountered in death investigation and human performance toxicology casework in the authors' laboratories.

Novel hallucinogens

Introduction

Hallucinogens are naturally occurring or synthetic drugs of abuse producing hallucinations, dissociations and out-of-body experiences. Novel hallucinogens are characterized as chemical derivatives and analogs of classical hallucinogens, such as the psychedelic drug lysergic acid diethylamide (LSD) or the dissociative drugs ketamine and phencyclidine (PCP). These novel synthetic drug classes are derived from legitimate pharmaceutical research or experimentation by drug users seeking a novel experience. Descriptions of the structures, synthesis and effects of these substances are frequently found in online forums and relevant popular publications, such as *PiHKAL* (104) and *TiHKAL* (105). The body of peer reviewed literature and case reports of intoxications involving novel hallucinogens continues to grow. Adverse effects with toxicological findings from recent publications are compiled in Table V, including cases of hospitalization, death investigation and impaired driving.

Currently, the most commonly encountered novel hallucinogen subclass is the "NBOMe" series, which includes psychedelic compounds with administration routes and effects most similar to LSD. The term NBOMe is derived from the scientific nomenclature *N*-benzoyl-methyoxy. NBOMe's are structural derivatives of the 2 C phenethylamine series, including drugs such as 2C–I, 2C–B and 2C–E, first characterized in 1991 (133). NBOMe's achieved some popularity in the electronic dance music scene, but are currently decreasing in popularity (134). NBOMe's are typically purchased as a crystalline powder from clandestine sources or on the street as blotter tabs (135). According to the DEA Special Drug Testing and Research Laboratory, scientists have identified 33 NBOMe derivatives (136), of which only three are currently encountered: 25I-NBOMe, 25B-NBOMe and 25C-NBOMe. All three are currently Schedule I Controlled Substances in USA (137). Less frequently encountered novel hallucinogens include methoxetamine (MXE), methoxphenidine (MXP), DOC, 3-MeO-PCP and 4-MeO-PCP, none of which are mentioned by name to be Schedule I Controlled Substances in USA (137).

Pharmacology

NBOMe's, like the classical hallucinogen LSD, are agonists of the serotonergic system, binding to serotonin 5-HT_{2A} receptors. The pharmacological behavior of NBOMe's has been largely studied in comparison to other novel hallucinogens, finding potent 5-HT_{2A} receptor activity (138–140). 25I-NBOMe is described as a full agonist, while 25B-NBOMe and 25C-NBOMe are described as partial agonists. In research studies, 25I-NBOMe was shown to have potent serotonin 5-HT_{2A} receptor activity with a K_i of 0.044 ± 0.006 nM and an EC_{50} of 0.44 ± 0.07 nM (138), 25B-NBOMe was shown to have a K_i of 0.19 ± 0.01 nM (139), and 25C-NBOMe was shown to have a K_i of 0.9 nM (140). In human studies when taken orally, 25C-NBOMe was found to have the shortest onset from 0 to 15 min, followed by 25B-NBOMe from 20 to 70 min, and 25I-NBOMe from 15 to 120 min. Duration of effects lasted 6–10 h, with no significant difference between all three NBOMe's.

MXE, MXP and MeO-PCP, novel hallucinogens more closely related to ketamine and PCP, exhibit binding affinity at the *N*-methyl-D-aspartate receptor (NMDAR) (141–143). MXE was shown to have NMDAR affinity equal to or greater than ketamine with a K_i of 6.59 ± 0.06 nM (141). 2-MXP, 3-MXP and 4-MXP were shown to be relatively selective NMDAR antagonists with IC_{50} of 56.5 ± 5.8, 30.3 ± 2.6 and 723.8 ± 69.9, respectively; exhibiting

Table V. Novel hallucinogens case histories with clinical symptoms, autopsy findings and primary drug and additional drug concentrations

Drug	History	Clinical symptoms/ autopsy findings	Drug results (ng/mL unless specified)	References
25I-NBOMe	23 y/o F seen insufflating "synthetic LSD" and began exhibiting aggressive behavior, seizures and vomiting, before collapsing and becoming unresponsive.	Bruises and abrasions, congestion of lungs, mild pulmonary edema	Blood: 28 +25C-NBOMe and 25H-NBOMe at low concentrations	(106)
	18 y/o M presented to ED[a] after ingesting "2 hits of acid" in suicide attempt, stabbed himself in neck and chest.	Euphoria, tachycardia, visual hallucination, afebrile, mildly dilated pupils	Serum: 0.034 (11 h after ingestion)	(107)
	18 y/o M presented to ED after jumping out of a moving vehicle.	Severe agitation, hallucinations, tachycardia (HR[b] 150–160 bpm[c]), hypertension (BP[d] 150–170 mmHg systolic, 110 mmHg diastolic), required physical restraint, administered lorazepam	Serum: 0.76	(108)
	2 patients admitted to hospital for severe intoxication and admitted using 25I-NBOMe.	Severe agitation and hallucinations	Serum: 0.25 and 2.8	(109)
	Case 1: 21 y/o M attended a rave party and admitted to taking "2 hits of acids." Fell into violent rage while driving, passenger pulled car over. Became unresponsive and pronounced dead at scene by EMS[e]. *Case 2:* 15 y/o F outside rave party and ingested unknown clear liquid. At home, she was flailing her extremities and became unresponsive. Taken to ED where she was pronounced dead.	*Case 1 Autopsy:* numerous contusions and ecchymosis; hemorrhaging, scattered petechiae, aspirated gastric contents in airways, moderate lung congestion and edematous *Case 2 Clinical:* Asystole with 39.9 °C rectal temperature *Case 2 Autopsy:* Isolated palpebral petechial hemorrhages, numerous abrasions and contusions; Copious foam in trachea and bronchi, moderate lung congestion	Cases 1 and 2 Blood: 25I-NBOMe	(110)
	18 y/o F presented to ED after seizures at a party, roughly 90 min after exposure.	Disoriented, agitation, confusion, GCS[f] 14, tachycardia (HR 145 bpm), hypertension (BP 145/100 mmHg), cutaneous flushing and hyperreflexia, administered lorazepam	Urine: 7.5 + 2C-I 1.8, 25H-NBOMe	(111)
	16 y/o M partying with friends and using drugs on blotter paper, found unresponsive in morning, pronounced dead.	Contusions and abrasions; severe and diffuse pulmonary edema, bronchial tree contained edematous fluid, mild cerebral edema	Post-mortem heart blood: 19.8 Urine: 25I-NBOMe	(112)
25B-NBOMe	18 y/o M ingested two squares of "NBOMe" with friends, became destructive, collapsed and became unresponsive, transported to ED; pronounced dead.	Lacerations, contusions and abrasions; severe and diffuse pulmonary edema, gastric contents present in bronchi	Post-mortem heart blood: 1.6 Urine: 25B-NBOMe	(112)
	16 y/o M presented to ED after three seizures and ingesting what he thought was LSD.	GCS 9, postictal, intubated and administered morphine and midazolam	Blood: 0.089 22 h after ingestion	(113)
	10 Patients admitted to ED for injection of 25B-NBOMe.	Agitation (10), hallucinations (10), panic (5), dilated pupils (10), tone increased (5), inducible clonus (3), sweaty (8), restraint (8), temperature 36.6–38.0°C, HR 100–175 bpm, BP 120–200/65–100 mmHg, administered midazolam (7)	Plasma: 0.7–10.1 Urine: 2.6–178	(114)
	19 y/o M found by roommates with "jerking movements." EMS arrived, reported unresponsiveness and grand mal seizure before transport to ED.	Status epilepticus, tonic-clonic jerking movements, rectal temperature 40°C, HR 152 bpm, respiratory rate 22/min, BP 145/90 mmHg, administered lorazepam	Serum: 0.18 Urine: 1.9	(115)
	17 y/o M and 31 y/o M ingested drug labeled "NBOMe."	Confusion, agitation, hypertension, tachycardia, hyperthermia, sweating, dilated pupils, administered benzodiazepines	Urine: qualitative	(116)

Table continues

Table V. Continued

Drug	History	Clinical symptoms/ autopsy findings	Drug results (ng/mL unless specified)	References
25C-NBOMe	24 y/o F ingested three blotter paper doses of what she thought was LSD, experienced hallucinations, and was transported to hospital.	Tachycardia, tachypnea, agitated delirium, confusion, dilated pupils, disorientation	Blotter paper: 25C-NBOMe +2C-I trace	(117)
	22 y/o M died at hospital after insufflating "25C-NBOMe" purchased from internet. Talking incoherently, running around apartment, had jerky movements and a clenched jaw. When ambulance arrived, he was unconscious.	Hallucinations, convulsions, mydriasis, hyperthermia, diffuse bleeding from mucosa, respiratory and metabolic acidosis, rhabdomyolysis, anuria, hyperkalemia, low BP; organ congestion, fluid in thorax and abdomen, diffuse mucosal hemorrhage	Anti-mortem blood: 0.81 µg/kg Post-mortem blood: 0.60 µg/kg Urine: 2.93 µg/kg Vitreous: 0.33 µg/kg Liver: 0.82 µg/kg Gastric contents: 0.32 µg/kg total	(118)
MXE[g]	Driver stopped for DUID.	*DRE*[h] *evaluation:* thick, slurred and deliberate speech; red, watery and bloodshot eyes; blank, vacant expression; slow and deliberate movements; hard time understanding simple questions; twitching, uncontrolled movements	Blood: 10	(119)
	19 y/o M, with hx of drug abuse, psychosis, depression and ADHD, self-administered unknown IV dose. 30 min after ingestion he presented at ED.	Confusion, extreme agitation, semi-stupor, tachycardia, hypertension, ataxia, mydriasis, nystagmus, resolved with systematic treatment	Serum: MXE	(120)
	35 y/o M presented at ED after collapsing. Unresponsive by EMS and bleeding from nostril. Small packet found in pocket labeled with MXE structure.	*Clinical:* hypertensive, not tachycardic, bilateral pupillary mydriasis, condition impaired	Powder: MXE	(121)
	33 y/o F DUID pulled over after near collision.	*DRE evaluation:* rigid muscle tone, confused, unresponsive	Blood: 160	(122)
	29 y/o M, with history of alcohol and NPS abuse, found dead at home.	N/A	Blood: 5,800 Urine: 85,000	(123)
	31 y/o M in poor condition is transported to hospital and falls into deep coma, died 4 weeks after ingestion.	*Clinical:* acute respiratory failure, hyperthermia, generalized seizures, leukocytosis, massive rhabdomyolysis, hepatic failure, onset of acute renal failure	Serum: 320	(124)
	21 y/o M, with hx of substance abuse but not known to be epileptic, found collapsed in bedroom. EMS called and taken to hospital.	*Clinical:* sinus bradycardia, creatinine kinase, hyponatremia, lateral bite of tongue	Serum: 30 Urine: 408	(125)
	28 y/o M	Confusion, hallucinations, extreme agitation, aggression, tachycardia (HR 120 bpm), normal BP (130/80 mmHg), administered benzodiazepines, experienced amnesia	Serum: 270 Urine: 660	(126)
MXP[i]	33 y/o M impaired driver crashed his vehicle, with vague memories of crash. Police suspected alcohol but breath test negative.	*DRE evaluation:* confused, agitated, inconsistent driving style, delayed response, restlessness, fast choppy erratic speech	Serum: 57 (2 h after incident)	(127)
	Case 1: 34 y/o M found dead at home with powder nearby, identified as MXP. *Case 2:* 34 y/o M found dead at home with hx of epilepsy, powder found in pocket *Case 3:* 38 y/o M died after jumping from a bridge, has schizophrenia.	*Case 1 autopsy:* enlarged heart, hypertensive heart disease *Case 2 autopsy:* moderately enlarged heart, mild atheroma	Case 1 Femoral Blood: 24,000 Case 2 Femoral Blood: 2,000 Case 3 Femoral Blood: 1,360 (alternate cause of death)	(128)

DOC[j]	37 y/o M found dead at home with early stages of decomposition.	Pulmonary edema and subgaleal hemorrhage	Iliac Blood: 377 Urine: 3,193 Liver: 3,143 ng/g Brain: 683 ng/g	(129)
	18 y/o M came home with agitation and hallucinations, then unresponsive, shaking in extremities. Mother called EMS. Presented to ED with status epilepticus.	Seizures, left gaze deviation, dilated pupils, abnormal extremities movement, tachycardia, tachypnea, prolonged QT interval, tonic head turning	Serum: 3 (5.5 h after ingestion)	(130)
3-MeO-PCP	29 y/o M with hx of illicit drug use found unresponsive in bed with clear fluid leaking from nose and mouth. He was pronounced dead at hospital.	Congested lungs, bladder distended with urine, moderate atherosclerosis, no signs of trauma	Blood: 139 ± 41 +PCP ELISA Screen: Positive	(131)
4-MeO-PCP	54 y/o M, with psychiatric illness and drug abuse hx, found unresponsive in bed. Pronounced dead at scene.	Pulmonary congestion and edema, foam in airways and mouth, mildly enlarged heart, congestive hepatosplenomegaly and minimal hepatic steatosis, no traumatic injuries	Peripheral blood: 8,200 Central blood: 14,000 Liver: 120 mg/kg Vitreous: 5,100 Urine: 140,000 PCP ELISA screen: Positive +4-HO-MET in blood	(132)

[a]Emergency department.
[b]Heart rate.
[c]Beats per minute.
[d]Blood pressure.
[e]Emergency medical services.
[f]Glasgow coma scale.
[g]Methoxetamine.
[h]Drug recognition expert.
[i]Methoxphenidine.
[j]2,5-Dimethoxy-4-chloroamphetamine.

a similar profile to 2-, 3- and 4-MeO-PCP analogues (142). Additionally, this report finds that 2-MXP is less potent *in vivo* than PCP and ketamine. 3-MeO-PCP was shown to have the greatest binding affinity at NMDAR over 2- and 4-MeO-PCP, with similar potency to PCP (143).

NBOMe's

NFLIS in a 2015 report (144) lists 25I-NBOMe, 25C-NBOMe and 25B-NBOME as among the top phenethylamine compounds encountered in the United States. 25I-NBOMe (Figure 1) is currently the most prevalent NBOMe derivative according to the EMCDDA, with first identification occurring in Sweden in May 2012 (145). After 25I-NBOMe ingestion and hospitalization (111) and hepatocyte studies (146), demethylated metabolites and 2C–I were identified. Recent ingestion of 25I-NBOMe resulted in hospitalizations and drug-related fatalities. Common behavior prior to and during hospitalizations include agitation, aggression, violent thrashing, seizures, vomiting, euphoria, visual and auditory hallucinations and unresponsiveness (106–108, 110–112, 117, 147). Hospital personnel reported tachycardia, mydriasis, hypertension, normal temperature, hyperpyrexia, metabolic acidosis, clonus, asystole, elevated white blood cell count and elevated creatinine kinase in patients (107, 110, 111, 147). Abrasions and bruising from agitated and aggressive behavior, as well as lung congestion, pulmonary edema and hemorrhaging (106, 110, 112) were reported at autopsy. Toxicological findings from NBOMe's in blood, serum and urine are in Table V.

25B-NBOMe is the next most prevalent NBOMe, and was first reported by Sweden in December of 2012 (148). 25B-NBOMe is structurally identical to 25I-NBOMe except for the halogen, leading to similarly reported behavior and adverse effects. 25B-NBOMe intoxications were associated with hospitalizations and drug-related fatalities. Following ingestion, medical personnel reported seizures, hallucinations, violent agitation, aggression and unresponsiveness (113–115). During hospitalization, mydriasis, tachycardia, hypertension, hyperthermia, sweating, convulsions, rhabdomyolysis and deranged liver function were observed (114, 116). Autopsy personnel report external lacerations, contusions and abrasions, as well as severe and diffuse pulmonary edema (112).

25C-NBOMe was first reported by Finland in June of 2011 (148). Like 25B-NBOMe, 25C-NBOMe differs in the halogenated species and has similarly reported effects to the NBOMe class. 25C-NBOMe intoxications were associated with hospitalizations and drug-related fatalities. Prior to arrival at hospital, behavior consisted of seizures, loss of consciousness, incoherency, hallucinations, jerky movements and jaw clenching (118, 149). In hospital, medical personnel reported tachycardia, tachypnea, agitated delirium, mydriasis, disorientation, convulsions, diffuse bleeding from all mucosa, respiratory and metabolic acidosis, rhabdomyolysis, anuria, hyperkalemia and low blood pressure (118, 149). Autopsy results concluded organ congestion, fluid in thorax and abdomen and diffuse mucosal hemorrhaging (118).

Methoxetamine

Other novel hallucinogens exhibit more dissociative like properties, similar in nature to ketamine and PCP. Methoxetamine (MXE, M-Ket, METH-O, MEXXY) (Figure 1) is structurally similar to ketamine, producing behavior and effects similar to ketamine and PCP; however, according to users, methoxetamine exhibit delayed onset and has longer lasting effects (150). Methoxetamine, like other NPS, is sold online in dark web markets as a white crystalline powder (151) and was first identified by the EMCDDA in September of 2010 (152). There are no human methoxetamine administration studies, but important data are available from clinical and forensic cases.

Following methoxetamine ingestion, users were confused, agitated, hallucinating and unresponsive (120). In one case, methoxetamine exhibited a ketamine-like dissociative state, but with added entheogenic and euphoric elements (121). Upon admission to hospital, documented adverse effects included tachycardia, hypertension, ataxia, mydriasis, nystagmus, leukocytosis, massive rhabdomyolysis, hepatic failure, onset of acute renal failure, sinus bradycardia, elevated creatinine kinase and hyponatremia (120, 121, 124–126). These effects are similar to ketamine-like adverse effects and were resolved with symptomatic treatment in one case (120). Another patient presented to hospital with a Glasgow Coma Score (GCS) of 14 after 20 min, and 15 after 90 min, but conditions improved and the patient survived (121).

In a methoxetamine polydrug DUID case, the driver was operating a vehicle with a flat tire and was pulled over for questioning. A DRE officer performed standard field sobriety tests (SFST) noting slurred speech, bloodshot eyes, a blank expression, lack of understanding and uncontrollable motor movements. This led to the arrest of the subject and a subsequent blood collection. Analysis revealed low concentrations of clonazepam, 7-aminoclonazepam, 11-nor-9-carboxy-THC (THCCOOH), diphenhydramine and MDMA, and significantly 10 ng/mL methoxetamine (119). Another DUID case involved a driver pulled over following a near collision. When stopped, the driver needed assistance from the officer to place the vehicle in park. The office noted the driver to be confused and unresponsive at times, exhibiting rigid muscle tone. Following collection and analysis of blood, the methoxetamine concentration was determined to be 160 ng/mL (122).

Literature has been published involving drug-related fatalities with methoxetamine (123, 153), but these sources provide no physiological data at autopsy, only biological drug confirmation. All toxicological findings from hospitalizations, drug-related deaths and DUID investigations involving methoxetamine concentrations in blood, serum and urine are found in Table V.

Methoxphenidine

The newly emerging novel hallucinogen methoxphenidine (MXP) (Figure 1) is structurally related to diphenidine, another novel hallucinogen, and is more commonly associated with PCP-like effects than methoxetamine, as suggested by its name. In a DUID investigation, a driver crashed his car into a railway-crossing gate with no recollection of the incident. When police arrived, the officer noted the driver was confused, agitated and suffered from memory loss, in addition to delayed responses and restlessness. Following further engagement and interaction, the officer observed the driver's speech to be fast, choppy and erratic, but the alcohol breath test was negative. Serum laboratory results were amphetamine (111 ng/mL), MDMA (28 ng/mL), MDA (3 ng/mL) and methoxphenidine (57 ng/mL) (127).

The first reported methoxphenidine fatalities were in 2015. Two individuals were found dead at home with white powders nearby, positively identified as 2-methoxphenidine. Enlarged heart, hypertensive heart disease and mild atheroma were found at autopsy, with femoral blood concentrations of 24 and 2 mg/L. Another individual found dead after jumping from a bridge, had a femoral blood concentration of 1.3 mg/L. Analysis of urine samples in these cases identified the hydroxyl-methoxphenidine metabolite (128).

2,5-Dimethoxy-4-chloroamphetamine

2,5-Dimethoxy-4-chloroamphetamine (DOC) (Figure 1) is a ketamine-like hallucinogen, structurally related to the 2C phenethylamine series mentioned above. DOC was reported in drug seizures in Florida in 2016 (154), and its effects were well characterized in *PiHKAL* (104) in 1991. As previously mentioned, DOC is not specifically controlled in USA (137), but could be considered controlled as an analogue of DOB and DOM, which are on the Schedule I Controlled Substances list. In one case report (130) medical personnel reported individuals, having used DOC, displaying agitation and hallucinations, followed by unresponsiveness, in a patient with tachycardia, tachypnea, prolonged QT interval, abnormal movements, tonic head turning and gaze deviation. After administration of midazolam and lorazepam, the patient improved over time. Serum DOC concentration was 3 ng/mL after 5.5 h. The first reported DOC fatality involved a decomposed individual found dead at home in 2014 (129). The fatality was reported as an acute intoxication with DOC concentrations of 377 ng/mL iliac blood, 3,193 ng/mL urine, 3,143 ng/g liver and 683 ng/g brain.

3-Methoxy-phencyclidine

Novel hallucinogens 3-methoxy-phencyclidine (3-MeO-PCP) (Figure 1) and 4-methoxy-phencyclidine (4-MeO-PCP), for general purposes referred to as MeO-PCP, are methoxy-substituted positional isomers and chemical derivatives of the traditional hallucinogen PCP. MeO-PCP derivatives were first synthesized in the 1960s and 1970s (155), but the first fatalities were not reported until 2014 from Sweden (156). 3-MeO-PCP and 4-MeO-PCP are not explicitly controlled in USA (137), but would be considered analogs of PCP, federally controlled by the DEA. In one 3-MeO-PCP and one 4-MEO-PCP fatal case, the decedents were found unresponsive, with liquid or foam in the mouth and airways (131, 132). At autopsy, both individuals were determined to have pulmonary congestion, and in one case edema, with no signs of visible trauma. Blood samples in each case produced positive enzyme-linked immunosorbent assay (ELISA) PCP screening results. The 3-MeO-PCP case also mentioned distended bladder and moderate atherosclerosis, and was reported as a combined drug intoxication. Blood 3-MeO-PCP concentration was 139 ± 41 µg/L, with diphenhydramine at 4.1 ± 0.7 mg/L (131). The report from the 4-MeO-PCP fatality (132) included an enlarged heart, congestive hepatosplenomegaly and hepatic steatosis, with 4-MeO-PCP concentrations of 8.2 mg/L peripheral blood, 14 mg/L central blood, 120 mg/kg liver, 5.1 mg/L vitreous and 140 mg/L urine. In addition to 4-MeO-PCP, this case qualitatively reported 4-hydroxy-*N*-methyl-*N*-ethyltryptamine, another novel hallucinogen.

Discussion

Recently reported novel hallucinogens, with documented adverse effects and toxicological confirmations, consist of 25I-NBOMe, 25B-NBOMe, 25C-NBOMe, methoxetamine, methoxphenidine, DOC, 3-MeO-PCP and 4-MeO-PCP. Although these drugs are classified under one NPS class, documented adverse effects differ based on the specific novel hallucinogen ingested. NBOMe's displayed adverse effects including episodes of agitation and aggression leading to noticeable bodily harm markings in autopsy findings. These effects were not documented with other novel hallucinogen use. The most common physiological effect during hospitalization was tachycardia, seen with all novel hallucinogens. Some NBOMe users were agitated and/or aggressive and responded positively to benzodiazepine (midazolam, lorazepam or diazepam) administration (113, 114). Novel hallucinogens are also of concern in cases of excited delirium (157), as reported during police-involved incidences.

Currently, no standard laboratory practices exist for novel hallucinogens in analytical testing procedures. In a survey of laboratories performing DUID testing (n = 70), 83% of laboratories are confirming PCP in blood at 10 ng/mL and 78% PCP in urine at 10 ng/mL (158). Additionally, only 50% of laboratories routinely test for ketamine, and 89% are not routinely testing for LSD. When asked what additional compounds should be added to the recommended scope for DUID testing, only one laboratory listed NBOMe's. Although hallucinogens are not among the top drugs detected in DUID investigations, these data strongly suggest the need for testing for novel hallucinogens in fatalities and DUID investigations based on case investigative information. Analytical confirmation scopes during death investigations are not currently available, as with the DUID survey.

With the current state of novel drug markets, laboratory personnel need to consider the challenges and limitations of testing for novel hallucinogens. There are reports of ELISA and homogenous immunoassay cross-reactivity with traditional hallucinogen screens (131, 132), specifically MeO-PCP derivatives with PCP kits, providing useful analytical information for novel hallucinogen identification. Novel hallucinogens identified in this review should be incorporated into screening applications, where applicable, most notably time-of-flight mass spectrometry. Collected information from monitoring online drug forums has accounted for more the 60 novel dissociatives and psychedelics being discussed by drug users within the last two years. While all of these drugs will not be identified in toxicology laboratories, it is important to understand the evolving drug markets and to remain current with literature on novel hallucinogen intoxications and fatalities.

Designer benzodiazepines

Introduction

In 2013, the EMCDDA and Europol published a joint response to the recent illicit drug market in the European Union (EU) focusing on NPS (159). Due to the diversity of NPS seen in the online market, the EMCDDA introduced six new NPS categories, based on chemical similarity and mode of action, including the designer benzodiazepines. Many designer benzodiazepines were initially synthesized by pharmaceutical companies in the 1960s and 1970s as therapeutic drug candidates, but were not developed, forwarded to clinical trials or approved for medicinal use (160). Benzodiazepines are frequently ingested to counteract withdrawal symptoms from stimulant and hallucinogenic drugs and for anxiety disorders, when a prescription cannot be obtained. Designer benzodiazepines are a public safety concern, due to their high potency, with low doses producing strong sedation and amnesia leading to unintended overdosing. Table VI summarizes reported designer benzodiazepine fatalities, DUID cases and overdoses.

Pharmacology

Designer benzodiazepines are pharmacologically similar to traditional benzodiazepines, acting as agonists at the $GABA_A$ receptor. Documented and reported effects mimic those of traditional benzodiazepines, causing loss of coordination, drowsiness, dizziness, blurred vision, slurred speech, amnesia and in some cases, death. Detailed pharmacologically behavior of specific designer benzodiazepines can be found below.

Phenazepam

Phenazepam ("Zinnie") (Figure 1) is a benzodiazepine developed in the Soviet Union in the 1970s and is widely used in Russia and other former eastern bloc countries for the treatment of epilepsy, anxiety and sleeping disorders. Therapeutic phenazepam concentrations are 20–60 ng/mL following a 0.5–2 mg clinical dose (170). Phenazepam is not currently scheduled or prescribed in USA or in most of Western Europe, but is easily accessible through internet markets (171, 172). Phenazepam shares its pharmacology with other benzodiazepines as an agonist at the $GABA_A$ receptor (161, 173) and is ~5–10 times more potent than diazepam (171, 172). The drug has a half-life of up to 60 h, and the onset of action occurs within 2–3 h. Peak phenazepam blood concentrations after 3 and 5 mg oral doses were 24 and 38 ng/mL, respectively, ~4 h after dosing. Reported side effects of phenazepam ingestion include: loss of coordination, drowsiness, dizziness, blurred vision, slurred speech, amnesia and ataxia (161, 173).

Phenazepam was one of the first novel benzodiazepines to appear in the illicit drug market; in April 2014, the DEA reported 284 phenazepam seizures in 31 states from 2008 to 2013 (173). In 2013, the Georgia Bureau of Investigation's Division of Forensic Sciences reported 11 cases of impaired drivers under the influence of phenazepam from March 2010 to August 2011 (161). In five of these cases, phenazepam was the only toxicological finding and in six, additional drugs were detected. The cases included nine males and two females with an average and median age of 26 (±7) and 24 years, respectively. Their phenazepam blood concentrations ranged from 40 to 3,200 ng/mL, with a median of 170 ng/mL and an average of 500 ng/mL. If the single high concentration of 3,200 ng/mL is excluded, the average was 230 ng/mL. For the phenazepam only cases, the median (range) concentration was 80 (40 to 3,200) ng/mL and the average 690 ng/mL. The mean concentration was 96 ng/mL, when excluding the 3,200 ng/mL high concentration. Three of the concentrations were below the assay's lower limit of quantification (100 ng/mL) and were estimated. The most common impairment observations in field sobriety tests in other phenazepam cases were slow and slurred speech, lack of balance and disorientation. Table VI contains detailed information about these 11 cases.

Phenazepam also is misused in Europe. The UK banned importation of phenazepam in July 2011. Also in July 2011, the UK Advisory Council on the Misuse of Drugs (ACMD) submitted phenazepam as a Class C compound under the UK Misuse of Drugs Act (174). Phenazepam is currently controlled in Denmark, Norway, Finland and Lithuania (162). In 2013, an individual insufflated ~1 g of three different white powders purchased from the internet. Within 30 min, he was confused and disoriented; he was taken to the emergency department when symptoms did not resolve within 16 h. Symptoms displayed during his initial evaluation and toxicological findings are included in Table VI.

Etizolam

Etizolam (Depas®) (Figure 1) was introduced in 1983 in Japan as a prescribed benzodiazepine for the treatment of anxiety and muscle relaxant properties. It is approved in Japan, Korea and Italy, but not in the US. Etizolam is chemically and pharmacologically similar to diazepam, but 6–10 times more potent based on preclinical data (175). The drug has a short half-life of 3.4 h, and is rapidly absorbed after oral administration, with peak plasma concentrations (T_{max}) at 0.5–2 h. In clinical studies, a single 2 mg oral dose produced a mean C_{max} of 25 ng/mL (variability not provided) (176). Reported adverse effects included drowsiness, sedation, muscle weakness and incoordination, fainting, headache, confusion, depression, slurred speech, visual disturbances and changes in libido and tremors. From 2012 to 2014, the DEA had 140 etizolam seizures from 21 states (175). The American Association of Poison Control Centers showed an incremental increase in etizolam related cases each year since 2011, with 41 cases reported in August 2014. In 2012, an individual was found unresponsive with bradypnea next to an empty syringe (163). Emergency personnel also were told he ingested many etizolam tablets. In route to the emergency department, he was administered a 0.2 mg dose of intranasal naloxone that improved his respiratory rate, but not his mental status. His vital signs upon arrival at the hospital are shown in Table VI. Due to continued sedation, 0.2 mg intravenous flumazenil, a benzodiazepine antagonist, was administered producing immediate and complete reversal of sedation. Two hours after admission, he received an additional 2 mg intravenous dose of naloxone after becoming somnolent and bradypneic. He was discharged 8 h after admission with full resolution of his mental status.

Flubromazolam

Flubromazolam (Figure 1), the triazolo analogue of flubromazepam, may be more potent than flubromazepam, although preclinical and in vitro data are lacking (177). In 2015 in Poland, a 27-year-old man known to experiment with NPS, was found unconscious at home (166). The family disclosed that he recently obtained unknown drugs. Vital signs upon arrival to the emergency department and serum and urine flubromazolam concentrations are included in Table VI. His low blood pressure was not improved with fluids, 25 mg epinephrine or a 0.4 mg naloxone dose twice every 3 min. The urine drug screen was positive for benzodiazepines, resulting in administration of 0.5 mg injected flumazenil twice every three min. Flumazenil increased the GCS score to 10, but 30 min later it deteriorated to 3. After 4 days of hospitalization, the patient was stable enough to be extubated and on the ninth day of treatment was moved to a neurology treatment facility. The patient disclosed that 48 h before admission he ingested 2 mg flubromazolam and PCP. He was sleepy but he woke up after ~10 h and ingested another 3 mg flubromazolam 19 h before hospitalization.

An individual in Virginia ingested multiple small round candies and became unresponsive (167). The individual was revived by friends throughout the night and the following morning was admitted unresponsive to the hospital, where the individual died. The candies contained heroin and flubromazolam. Flubromazolam concentrations in the admission serum and urine samples, and other analytical findings are provided in Table VI.

Designer benzodiazepines in blood—no case histories

In Norway, blood samples were collected from 22,022 criminal offenders from July 1, 2013 to May 31, 2016 (164). Within this population, 77 cases (0.3%) contained clonazolam, diclazepam, flubromazepam, flubromazolam, pyrazolam and/or etizolam. Of all, 69 were DUID cases, with 14 traffic crashes. One designer benzodiazepine was found in 69 (90%) of cases, with the remaining containing two or three designer benzodiazepines. Overall, 68 cases were males (88%) and 9 were females (12%), with a median age of 27 (17–62) years. Median and range of benzodiazepine concentrations are reported in Table VI. Of the 77 cases, the only toxicological findings in six cases were a designer benzodiazepine, with four of these drivers charged with DUID. The clinical test of impairment

Table VI. Novel benzodiazepines case histories with clinical symptoms, autopsy findings and primary drug and additional drug concentrations

Drug	History	Clinical symptoms/autopsy findings	Drug results (ng/mL unless specified)	References
Phenazepam	18 y/o M driver crashed after ignoring crossing guard signaling to stop	*Officer observations:* Lethargic, slurred speech, lack of balance, red conjunctiva *Clinical observation:* abnormal HR[a]	Blood: 180 +THCCOOH 28	(161)
	27 y/o M stopped by police after failing to maintain lane	*Officer observations:* Slow reactions, slurred speech, disorientation, drowsiness, lack of balance, pupils slow to react to light; HR 111 bpm[b]	Blood: 500 +Cyclobenzaprine 6.1	(161)
	22 y/o M stopped by police after leaving crash scene and hit mailbox	*Officer observations:* Slurred speech, lack of balance	Blood: 750 +Trazodone (qualitative)	(161)
	29 y/o F stopped by police for failure to maintain lane after almost colliding with another car	*Officer observations*: Constricted pupils, slurred speech, red conjunctiva, lack of balance *Field sobriety tests:* Walk and turn, missed heel to toe; OLS[c], body sway and put foot down; Romberg, estimated 37 s for 30 s	Blood: 310 +Amphetamine 190 and quetiapine (qualitative)	(161)
	39 y/o M found in car in parking lot with crash damage	*Officer observations:* Slow mumble speech, confusion, lack of balance *Field sobriety tests:* HGN[d], lack of smooth pursuit; nystagmus prior to 45° and at maximum deviation in both eyes	Blood: 170 +THCCOOH in urine	(161)
	23 y/o M in multi-car crash after driving through stop sign	*Officer observations:* Slurred speech, disoriented, sedated *Field sobriety tests:* HGN, lack of smooth pursuit, nystagmus detected prior to 450 and at maximum deviation in both eyes; Walk and turn, missed heel to toe, used arms for balance	Blood: 140 +gabapentin (qualitative)	(161)
	22 y/o M drove off road and hit tree in single car crash	*Officer observations:* Memory loss, disoriented, dilated pupils, slurred speech	Blood: 3,200	(161)
	40 y/o M stopped by police for failing to maintain lane and driving with flat tire	*Officer observations:* Confusion, constricted pupils, slurred speech *Field sobriety tests:* HGN and VGN[e], lack of smooth pursuit; Walk and turn, missed heel to toe; OLS, raised both arms for balance, put foot down	Blood: ~40	(161)
	24 y/o F crashed into back of car at stop light	*Officer observations:* Lethargic, intoxicated *Clinical observations:* HR 150 bpm	Blood: ~50	(161)
	29 y/o M ran out of gas in middle of road, stumbling in road trying to flag down cars	*Officer observations:* Lack of balance *Field sobriety tests:* Romberg, swayed and almost fell; Walk and turn, failed to touch heel to toe, took wrong # steps, stepped off line; OLS, put foot down, swayed	Blood: 120	(161)
	21 y/o M drove car off road in single car crash	*Officer observations:* Lethargic, intoxicated *Field sobriety tests:* HGN, lack of smooth pursuit, nystagmus detected prior to 450 and at maximum deviation in both eyes; Walk and turn, missed heel to toe, stepped off line, too many steps; OLS, put foot down, used arms for balance, swayed	Blood: ~80	(161)
	42 y/o M insufflated ~1 g of three white powders	*Clinical observations:* Confused, disoriented, normal pupils, temperature, BP[f] and HR	Serum: 490	(162)
Etizolam	31 y/o M ED[g] admission after found unresponsive and bradypneic next to empty syringe of alleged heroin	*Clinical observations:* HR 115 bpm, respiratory rate 12 breath/min, BP 132/64 mmHg, temperature 98.9°F	Serum: 103 +Urine: codeine 322, morphine >1,000, 6-AM 272	(163)
	DUID Cases ($n = 14$)	N/A	Blood: Median 50 (1.9–170)	(164)
	Deidentified urine cases (Sweden) ($n = 11$)	N/A	Urine: 5.8–270	(165)
Flubromazolam	27 y/o M experimented with NPS, found unconscious at home	Hypotensive (BP 80/40 mmHg), tachycardic (HR 102 bpm), deep coma (GCS[h] 3), hypoventilation (6–8 breaths/min)	Serum: 59 Urine: 105	(166)
	Individual ingested small round candies and became unresponsive	Unresponsive, later died	Blood: 20 Serum: 18 Urine: 48	(167)

Table continues

Table VI. Continued

Drug	History	Clinical symptoms/autopsy findings	Drug results (ng/mL unless specified)	References
			+serum: morphine 19; urine positive for morphine, codeine, 6-AM	
	DUID cases (n = 25)	N/A	Blood: median 12 (0.4–100)	(164)
	Deidentified urine cases (Sweden) (n = 96)	N/A	Urine: 5.4–1,500	(165)
Clonazolam	20 y/o M with hx anxiety and depression found unresponsive in car after ingestion of "Pinzor" tablets	Stable upon ED arrival, hypotensive (BP 79/46 mmHg) and bradycardic (HR 51 bpm)	Urine: 60	(168, 169)
	18 y/o M found unresponsive in car after ingestion of "Pinzor" tablets	Stable upon ED arrival, hypertensive (BP 174/107 mmHg) and tachycardic (HR 135 bpm)	Urine: 34 +THC and morphine qualitative	(168, 169)
	DUID cases (n = 7)	N/A	Blood: median 5.3 (1.9–11)	(164)
	Deidentified urine cases (Sweden) (n = 8)	N/A	Urine: 7.3–23	(165)
Diclazepam	DUID cases (n = *15)*	N/A	Blood: median 13 (2.1–57) ng/mL	(164)
Flubromazepam	DUID cases (n = 24)	N/A	Blood: median 55 (4.7–1,200)	(164)
	Deidentified urine cases (Sweden) (n = 9)	N/A	Urine: 2.7–30	(165)
Pyrazolam	DUID cases (n = 1)	N/A	Blood: 7.4	(164)
	Deidentified urine cases (Sweden) (n = 9)	N/A	Urine: 32–920	(165)
Meclonazepam	Deidentified urine cases (Sweden) (n = 45)	N/A	Urine: 1.6–190	(165)
Nifoxipam	Deidentified urine cases (Sweden) (n = 4)	N/A	Urine: 10–2,800	(165)
Deschloroetizolam	Deidentified urine cases (Sweden) (n = 1)	N/A	Urine: 130	(165)

[a]Heart rate.
[b]Beats per minute.
[c]One leg stand.
[d]Horizontal gaze nystagmus.
[e]Vertical gaze nystagmus.
[f]Blood pressure.
[g]Emergency department.
[h]Glasgow coma score.

performed by the physician who drew the blood sample determined that two individuals were considerably impaired one with 57 ng/mL diclazepam and one with 100 ng/mL flubromazolam.

Designer benzodiazepines in urine—no case histories

In Sweden, urine samples screening positive for benzodiazepines via cloned enzyme donor immunoassay (CEDIA), but not confirmed for prescribed benzodiazepines by liquid chromatography tandem mass spectrometry, were tested for 11 designer benzodiazepines (165). Three hundred and ninety samples collected from mid-February 2014 until November 2015 were tested for clonazolam, deschloroetizolam, diclazepam, etizolam, flubromazepam, flubromazolam, flutazolam, meclonazepam, nifoxipam, phenazepam and pyrazolam. A total of 40% (157) contained one or more designer benzodiazepines, but diclazepam, flutazolam and phenazepam were not detected. Urine concentrations are included in Table VI.

Flubromazepam

In 1962, Sternback *et al.* (178) first reported the synthesis of flubromazepam. Flubromazepam (Figure 1) is now an emerging designer benzodiazepine structurally related to phenazepam, with the only difference being a chlorine substituted for a fluorine atom (Figure 1). In Germany, a 42-year-old, 73 kg male self-administered one 4 mg capsule of flubromazepam. Symptoms of fatigue and enhanced desire for sleep lasted for three days. Fifteen serum and 25 urine samples were collected over 31 days. Peak flubromazepam serum concentrations were 78 ng/mL 6 h after ingestion. Flubromazepam half-life was ~106 h based on a one-compartment pharmacokinetic model (Kinectica software) and a non-compartmental analysis (Excel solver software).

Clonazolam

Clonazolam (Figure 1), first reported in 1970 by the Upjohn Company, is the triazolo analog of clonazepam and the most active of 17 compounds tested (177). The first cases of clonazolam intoxication in USA involved two males ages 18 and 20 found unresponsive in a car with additional clinical findings in Table VI (168, 169). Urine drug screen results were positive for benzodiazepines, with clonazolam confirmed concentrations listed in Table VI.

Diclazepam

Diclazepam (Figure 1) and diazepam, differing only by one chlorine atom, have equivalent potency (179). A 43-year-old, 73 kg male self-administered 1 mg oral diclazepam. Thirteen serum samples collected over 14 days and 46 urine samples collected over 21 days indicated a peak serum diclazepam concentration of 3.4 ng/mL 3 h after ingestion. A two-compartment model determined the half-life to be 42 h. Diclazepam also metabolizes to two pharmacologically active compounds, lorazepam and delorazepam. The 0.4 ng/mL peak lorazepam concentration occurred at 99 h and the peak 2 ng/mL delorazepam at 36 h.

Discussion

Traditional benzodiazepines display synergistic effects when ingested with alcohol, that can lead to coma or death, and those same effects are believed to occur with designer benzodiazepines due to their similar mechanisms of action. It can be seen in this review that the ingestion of designer benzodiazepines also leads to similar signs of impairment during driving as traditional benzodiazepines. Designer benzodiazepine diversity, widespread availability and increasing prevalence highlight the need for monitoring their use in forensic casework. It can be seen in the literature that these compounds are displaying cross-reactivity on traditional benzodiazepine immunoassay screening platforms; however, with the unavailability of standards to develop confirmatory assays the number of unconfirmed positives leads to inflated false positive rates. Forensic cases with a positive immunoassay result, but failing to confirm should be further investigated for the presence of designer benzodiazepines. The utility of screening samples using high-resolution mass spectrometry instrumentation, like time-of-flight, can aid in identification of designer benzodiazepines.

Designer opioids

Introduction

Between 2008 and 2013, the EMCDDA reported a 7-fold increase in seizures of NPS, with ~299 different substances monitored in 2013 (180). These included novel opioid receptor agonists, some of which are hundreds of time more potent than morphine, which lagged in their emergence in the street drug supply relative to synthetic cannabinoids and cathinones. These new synthetic opioids are of particular public health concern, due to their high potency and their distribution into the regular street heroin supply where they are often mixed with or substituted for heroin in spite of their much greater potency, leading to life-threatening respiratory depression and death. As these novel opioids emerge, emergency responders, medical professionals, law enforcement personnel, death investigators, medical examiners, toxicologists and prosecutors face the challenge of treating and investigating intoxications and deaths from novel compounds whose identities are often unknown.

Opioids of natural origin, such as morphine and codeine, and semisynthetic/synthetic opioids, such as fentanyl, are responsible for many serious adverse events including emergency department visits and fatalities. Although fentanyl was initially approved and prescribed as a new analgesic in 1960, illicit fentanyl and its analogs are a serious problem in USA (181, 182) and Europe (183). Recent case reports of overdoses, DUID cases and fatalities involving novel opioids are summarized in Table VII.

There are many chemical fentanyl derivatives, with alkyl and halo substituents on the phenyl group and varying alkyl chain length, many of which do not cross-react in routine immunological assays making them difficult to detect. Others do cross-react on ELISA but if they are not in the scope of a confirmatory assay, will result in screening false positives. In the last three years, numerous fentanyl analogs and derivatives, as well as non-traditional opioid agonists such as AH-7921, MT-45, U-47700 and other drugs originally synthesized and investigated by pharmaceutical companies as alternatives to morphine, have been introduced into the recreational opioid drug market in USA (210) and, in addition to being present in the heroin supply, they are also marketed as "research chemicals" over the internet.

Pharmacology

Fentanyl derivatives and the compounds named above are agonists at the μ, κ and δ opioid receptors based on preclinical data. These receptors are distributed widely in the brain, and are also found in the spinal cord and digestive tract. Activation of μ opioid receptors by an agonist such as morphine results in analgesia, sedation, euphoria, physical dependence, miosis, decreased respiration and

Table VII. Novel opioids case histories with clinical symptoms, autopsy findings and primary drug and additional drug concentrations

Drug	History	Clinical symptoms/autopsy findings	Drug results (ng/mL unless specified)	References
Acetyl fentanyl	28 y/o M prescribed oxycodone and pregabalin. In ED[a] after reportedly using fludiazepam.	Apneic, IV naloxone administered during ambulance transport.	Urine: 685 ng/mmol creatinine +urine: flubromazolam, pregabalin and oxycodone	(184)
	27 y/o M taken to ED after reported use of acetyl fentanyl.	Miotic pupils. Intubation and ventilator support required due to aspiration. 28-day ICU stay due to recurring severe agitation, delirium and hyperthermia.	Serum: 19.1 Urine: 85.5 ng/mmol creatinine	(184)
	22 y/o M taken to ED after ingestion of unknown NPS, clonazepam and alcohol.	7-day hospital stay. Pronounced rhabdomyolysis.	Serum: 14.8 Urine: 154 ng/mmol creatinine +7-amino clonazepam and ethanol	(184)
	37 y/o M taken to ED after insufflating drug. Individual was prescribed lorazepam.	Miotic pupils. IV naloxone given in ambulance.	Serum: 51 Urine: 235 ng/mmol creatinine +7-amino clonazepam, diclazepam, lorazepam, amphetamine, O-desmethyltramadol, methiopropamine, oxycodone and 2-AI	(184)
	20 y/o M taken to ED after oral ingestion of powder. Reported pregabalin, buprenorphine, clonazepam and amphetamine use.	Miotic pupils. Naloxone administered but insufficient response. 2-day hospital stay.	Serum: 0.6 Urine: 0.9 ng/mmol creatinine +7-amino clonazepam and pregabalin also detected	(184)
	21 y/o M taken to ED after ingesting acetyl fentanyl and maybe benzodiazepines.	Miotic pupils. IV naloxone administered in ambulance. 3-day hospital stay.	Serum: 32.7 Urine: 30.9 ng/mmol creatinine +2C-P, 4-FMC, 7-amino-clonazepam and 4-OH-alprazolam	(184)
	35 y/o F taken to ED. Suspected alprazolam and unknown NPS use.	Mydriasis. 2-day hospital stay.	Serum: 4.4 +clonazolam, oxazepam, amphetamine, 7-amino-nitrazepam, nitrazepam and ethanol	(184)
	40 y/o M taken to ED after suspected MDPV and PV use prior to death.	Apneic, tachycardic and cerebral hemorrhage progressing to cerebral edema.	Serum: 4.7 Urine: 47 ng/mmol creatinine +4F-PV8, α-PVT, dextromethorphan, amphetamine and fentanyl	(184)
	34 y/o M found dead in bed in supine position; vomit beneath head. Snoring at least 12 h before death. Police found "designer drugs" and insufflation straws.	Heavy organs (L and R lung, liver and brain were 590, 780, 1,610, 1,430 g). Cardiac hypertrophy with interstitial fibrosis and fatty infiltration of R ventricle indirectly contributed to death.	Cardiac blood: 270	(185)
	28 y/o M found unresponsive on bathroom floor with tourniquet around his arm and syringe nearby. Decedent had history of substance abuse, including anabolic steroids.	Needle track marks and foamy secretions from mouth. Pulmonary edema and mild diffuse cerebral edema.	Subclavian blood: 235 Liver: 2,400 ng/g Vitreous fluid: 131 Urine: 234	(186)
	24 y/o M found unresponsive by mother with uncapped syringe containing acetyl fentanyl and rubber tourniquet. Hx[b] of heroin abuse, with two previous overdoses.	Lungs edematous and congested (R 610 g and L 580 g). Three recent punctures in L forearm and antecubital fossa noted at autopsy.	Peripheral blood: 260 Central blood: 250 Liver: 1,000 ng/g Vitreous fluid: 240 Urine: 2,600	(187)
	Early 30s y/o M found unresponsive at home, pronounced dead at hospital. Hx of methamphetamine abuse. Acetyl fentanyl		Femoral blood: 153 Central blood: 239	(188)

	and 4-MeO-PV8 detected in pale brown-white powder and syringe.	Congested lungs and other organs, eyelid, capsula cordis and pleura petechiae and fluidity of heart blood. Two recent forearm needle marks.	Urine: 240 Gastric contents: 880 +4-MeO-PV8: femoral blood 389; central blood 960; urine 245; gastric contents 500 +7-aminonitrazepam 7,700; + phenobarbital 30 +methylphenidate, chlorpromazine and risperidone	
	20 y/o M found deceased in bed. EMS[c] pronounced dead at scene. Hx of illicit drug use.	No significant trauma. No anatomic cause of death.	Femoral blood: 192 Heart blood: 285 Liver: 1,100 ng/g Brain: 620 ng/g Urine: 3,420 +methoxetamine and fluoxetine in heart blood	(189)
	50 y/o F found unresponsive in bed. EMS pronounced dead. History of seizures, ethanol and prescription (hydrocodone, tramadol, gabapentin, celecoxib, cyclobenzaprine, venlafaxine, clonidine, buspirone, hydroxyzine and chlordiazepoxide) abuse.	External examination and toxicology testing only.	Femoral blood: 255 Heart blood: 210 Vitreous fluid: 140 Urine: 2,720 +heart blood venlafaxine, nordiazepam and chlordiazepoxide; femoral blood 2,000 venlafaxine	(189)
Butyryl fentanyl	30 y/o M in ED after reported MT-45 and flubromazepam use.	Decreased consciousness and tachycardia.	Urine: 8 +*N*-ethylbuphedrone, flubromazepam, 3-MeO-PCP, methiopropamine, MT-45, α-PBP, α-PPP and 4F-PVP	(190)
	24 y/o M in ED after reported drug intake	Sudden unconsciousness, apnea, respiratory depression, miotic pupils, hypothermia and suspected cardiac arrest. Required 2-day hospitalization.	Serum: 0.9 Urine: 65.6 +Serum fentanyl 4.3 +Urine fentanyl 993; cannabis and pregabalin	(190)
	23 y/o M in ED after nasal spray butyryl fentanyl and AB-FUBINACA.	Agitation, odd behavior, unpleasant feelings. Sudden unconsciousness, respiratory depression, myoclonus, dilated pupils, hyperthermia, hypertension and tachycardia.	Serum: 0.6 Urine: 2.0 +serum fentanyl 10.2 +urine fentanyl 118; *N*-ethylbuphedrone, 3-MeO-PCP, 4-MeO-PCP, α-PBP and pregabalin	(190)
	44 y/o M found unresponsive on bathroom floor. Syringe and drug paraphernalia at scene. Decedent had history of heroin abuse.	Needle marks in antecubital fossae, forearms, L wrist and ankles. Recent puncture on L antecubital fossa. Lungs edematous and congested (R 890 g and L 815 g).	Peripheral blood: 58 Central blood: 97 Liver: 320 ng/g Vitreous fluid: 40 Urine: 670 +peripheral blood acetyl fentanyl 38; central blood 32; liver 110 ng/g; vitreous 38; urine 540 and BE	(191)

Table continues

Table VII. Continued

Drug	History	Clinical symptoms/autopsy findings	Drug results (ng/mL unless specified)	References
	53 y/o F found unresponsive in bathroom. No drug paraphernalia. History of smoking, prescription drug abuse and psychiatric disorders hospitalization.	Lungs edematous and congested (L 450 g and R 510 g); mild atherosclerosis and L concentric ventricular myocardial hypertrophy.	Peripheral blood: 99 Central blood: 220 Gastric: 590 Brain: 93 ng/g Liver: 41 ng/g Vitreous fluid: 32 Bile: 260 Urine: 64	(192)
	45 y/o F found unresponsive in bed. History of anxiety, bipolar, disorder, previous suicide attempts and prescription drug and alcohol abuse. Only prescribed medications and expected pill counts found.	Lungs edematous and congested (L 570 g and R 680 g); mild L ventricular myocardial hypertrophy and mild nephrosclerosis.	Peripheral blood: 3.7 Central blood: 9.2 Gastric: 4,000 Brain: 63 ng/g Liver: 39 ng/g Vitreous fluid: 9.8 Bile: 49 Urine: 2 +acetyl fentanyl peripheral blood 21; central blood 95; gastric 28,000; brain 200 ng/g; liver 160 ng/g; vitreous 68; bile 330; urine 8 +peripheral blood alprazolam 40 and 0.11% ethanol.	(192)
	23 y/o M found unresponsive in bathroom. Tray with white powder and tube located at scene.	Cerebral edema and moderate full bladder. Residual white powder in nose. Fresh abrasions, bruising and fresh bleedings.	Peripheral blood: 66 Central blood: 39 Muscle: 110 ng/g Kidney: 160 ng/g Liver: 57 ng/g 120% increase in femoral blood concentrations taken 19 h apart, and 55% increase in heart blood	(193)
AH-7921	19 y/o M found deceased in bed. Friend reported decedent purchased two vials of unknown drug 2 nights earlier and reportedly used it night prior to death.	Frothy substance around mouth. Lungs congested and edematous (L 750 g and R 1,000 g). Liver and spleen enlarged (2,030 g and 370 g).	Peripheral blood: 9,100 Central blood: 3,900 Urine: 6,000 Bile: 17,000 Brain: 7,700 ng/g Kidney: 7,200 ng/g Liver: 26,000 ng/g	(194)
	Early 20s y/o M home from hospital after minor traffic accident with codeine and acetaminophen prescription. Decedent said he took six codeine tablets, and 3-MMC and 4-FMA powder from internet. After ingesting, on floor, began to snore and unresponsive.	Lungs edematous (2,080 g)	Peripheral blood: 430 +2-FMA 6.9; 3-MMC 2.1; codeine 420 and acetaminophen 18,700.	(195)
	Young F found deceased at home. Used needles and plastic bags labeled "AH-7921" and "etizolam" in trash.	Needle marks on R cubital fossa.	Peripheral blood: 330	(195)

			+methoxetamine 64, etizolam 270, phenazepam 1,330, 7-aminonitrazepam 43, diazepam 46, nordiazepam 73 and oxazepam 18	
MT-45	35 y/o M found deceased. Drug paraphernalia and two white powders confirmed as MT-45 and etizolam. No syringe. Hx of substance abuse.	Cerebral edema, pulmonary congestion and possible old injection site on foot.	Peripheral blood: 520 +etizolam 35 and diphenhydramine 220.	(196)
U-47700	23 y/o F in ED after insufflating and injecting "U-4". Responded to IV naloxone in field after failed IN dose.	Individual cyanotic with respiratory rate of 4 breath/min and pulse oximetry 60%. Non-cardiogenic pulmonary edema and hemoptysis.	Serum: 394 Urine: 228	(197)
	22 y/o M found apneic and unconscious after applying U-47700 and water to nostrils. CPR performed. Responded to IV naloxone in field.	Paramedics found patient cyanotic, respiratory rate of 4 breath/min and pulse oximetry 60%.	Urine: positive	(198)
	41 y/o F in ED for altered mental status after taking three illicitly purchased Norco pills. Responded to IV naloxone in ED.	Miotic pupils and respiratory depression.	Serum: 7.6 + serum fentanyl 15.2; Acetaminophen 10,032; BE 46; gabapentin 350, hydrocodone 107; and sertraline 15	(199)
	29 y/o M found unresponsive after injecting U-47700, regained consciousness before transport to ED. Admitted purchasing U-47700 and phenazepam online.	Physical examination unremarkable.	Serum: 240 Urine: Positive +serum (1,400) and urine phenazepam	(200)
	26 y/o M found lying on ground after consuming ethanol, alprazolam and insufflating "synthetic cocaine" purchased online.	Paramedics found patient cyanotic, pulse oximetry 50%. Pinpoint miotic pupils and tachycardia. Chest X-ray bilateral pulmonary consolidation. Mild acute kidney injury.	Urine: 0.1 +serum ethanol 0.055%	(201)
	24 y/o F fell asleep after consuming ethanol, alprazolam and insufflating "synthetic cocaine" purchased online. Called EMS after finding partner on ground.	Self-reported anxiety, nausea and abdominal pain to ED. Mild drowsiness noted.	Urine: Positive +serum ethanol 0.011%	(201)
	30 y/o M found deceased in home after vaporizing unknown powder identified as fentanyl and U-47700. History of substance abuse, including purchasing drugs online.	Pulmonary edema. Drug paraphernalia at scene.	Subclavian blood: 13.8 Urine: 17 +subclavian blood 10.9 fentanyl; 180 sertraline	(202)
	27 y/o M found deceased at home after snorting unknown powder. History of licit and illicit drug use, including cathinones and "legal highs".	No natural disease or cause of death.	Femoral blood: 1,460 +quetiapine 50; amphetamine <100; naproxen <800 +urine quetiapine, amphetamine, mexedrone, amitriptyline and ketamine.	(203)
	46 y/o M found at home unresponsive. Resumed consciousness ~1 h and admitted snorting a drug. Next morning found dead in bed. CPR performed, but pronounced dead at scene. Drug paraphernalia found. History of using drugs bought through mail.	Lungs edematous and congested (L 640 g and R 500 g). No puncture marks. Enlarged heart, liver and spleen (570, 2,310 and 300 g). 340 mL urine in bladder. Moderate obesity, pulmonary edema, atherosclerotic heart disease and fatty liver with fibrosis.	Peripheral blood: 190 Central blood: 340 Liver: 1,700 ng/g Vitreous: 170 Urine: 360 +Peripheral blood Alprazolam 120, nordiazepam <50, doxylamine 300, diphenhydramine 140, ibuprofen 2,400, salicylic acid <20 mg/L and THCCOOH 2.4	(204)

Table continues

Table VII. Continued

Drug	History	Clinical symptoms/autopsy findings	Drug results (ng/mL unless specified)	References
Furanyl Fentanyl	22 y/o M taken to ED after using furanyl fentanyl by nasal spray.	Received SC and IV naloxone.	Serum: 148 Urine: 85.2 ng/mmol creatinine +5-EAPB, MDPHP	(184)
	22 y/o M taken to ED after using nasal spray containing unknown drug and prescribed clonazepam.	Apneic and cyanotic. IV naloxone. Required 2-day stay in hospital.	Serum: 4.4 Urine: 9.2 ng/mmol creatinine +serum (11) and urine (51.3 9.2 ng/mmol creatinine) +MDPHP, pregabalin and clonazepam	(184)
4-Methoxy-butyryl fentanyl	29 y/o F taken to ED after suspected use of unknown NPS and prescribed tramadol.	Miotic pupils. Required 2-day stay in hospital.	Serum: 1.3 Urine: 5.1 ng/mmol creatinine +butyryl fentanyl, 4F-butyryl fentanyl, cannabis, nordiazepam tramadol, o-desmethyl-tramadol	(184)
	28 y/o M taken to ED after suspected unknown opioids and benzodiazepines intake.	Miotic pupils. IV naloxone. Required 2-day hospital stay.	Serum: 3.1 +4F-butyryl fentanyl, alprazolam, 4-OH-alprazolam, 7-amino clonazepam, BE, clonazepam, cocaine, O-desmethyltramadol, diazepam, oxazepam	(184)
	34 y/o M taken to ED after oral ingestion unknown tablets and prescribed fentanyl.	Temporarily apneic. Displayed miotic pupils. IV naloxone. Required 2-day hospital stay.	Urine: 11.9 ng/mmol creatinine +4F-butyryl fentanyl, clonazolam, GHB and fentanyl	(184)
4-Fluorobutyryl Fentanyl	25 y/o in ED after 4-fluorobutyryl fentanyl, pregabalin and clonazepam intake.	Disorientation, unsteadiness, slurred speech and hypotension.	Serum: 15.0 Urine: 9.5 +urine: pregabalin; tramadol; O-desmethyltramadol; 4-OH-alprazolam, oxazepam	(190)
Ocfentanil	24 y/o M found deceased at home. Drug paraphernalia, brown powder identified as ocfentanil, found at scene. History of illicit drug use. Nasal swabs indicated ocfentanil.	Lung and brain congestion. Distended bladder (300 mL).	Peripheral blood: 9.1 Heart blood: 27.9 Urine: 480 +peripheral blood: quetiapine <10, citalopram 130, THC 2.8 and >5 THCCOOH	(205)
	17 y/o M found deceased at home after snorting a brown powder identified as ocfentanil purchased online. Drug paraphernalia at scene. History of illicit drug use. Nasal swabs indicated ocfentanil.	N/A	Femoral blood: 15.3 Cardiac blood: 23.3 Liver: 31.2 mcg/kg Kidney: 51.2 mcg/kg Brain: 37.9 mcg/kg Vitreous humor: 12.5 Urine: 6.0 Bile: 13.7 +peripheral blood: acetaminophen 45 mg/L and caffeine 230	(206)

Mitragynine	17 y/o M found unresponsive in bed, pronounced dead at scene. Vomitus noted face and floor. Bali Kratom box found at scene and investigators obtained empty bottle of liquid Kratom. History of heroin abuse and chronic back pain, known to self-medicate with Kratom.	Lungs edematous and congested (combined weight 1,100 g). Distended bladder. No traumatic injury or anatomic evidence of potentially fatal natural disease.	Femoral blood: 600 +dextromethorphan 280, diphenhydramine 330, temazepam 210, 7-amino clonazepam 210	(207)
	Middle-aged M found deceased in bed after oral ingestion of Kratom purchased over internet. History of substance abuse and psychiatric disease. Urine drug testing throughout employment.	Lungs edematous and congested. Patchy bronchopneumonia. Heart enlarged. Moderate coronary atherosclerosis.	Femoral blood: 1,060 Urine: 3,470 +peripheral blood: zopiclone 43, citalopram 360, lamotrigine 5,400	(208)
	24 y/o M found in bed unresponsive after alcohol and "sleeping pill". CPR performed. Resuscitation unsuccessful. Vomitus on bedding and decedent's head. History of ethanol abuse, suicide attempts, depression and previous hospitalization for overdose.	Lungs edematous and congested (R 930 g, L 890 g). Distended bladder (300 mL). No natural disease or trauma.	Peripheral blood: 230 Central blood: 190 Liver: 0.43 mg/kg Vitreous fluid: <50 Urine: 370 +peripheral blood: venlafaxine 1,100, O-desmethylvenlafaxine 1,600, diphenhydramine 450, mirtazapine 240, ethanol 0.02%	(209)

[a]Emergency department.
[b]History.
[c]Emergency medical services.

decreased gastrointestinal motility which causes urine retention and constipation. Activation of κ receptors contributes to analgesia and sedation, but can result in some additional adverse side effects including dysphoria, depression and hallucinogenic/dissociative side effects, while δ receptors also contribute to analgesia and physical dependence. The human data for novel opioids derive from drug intoxications and fatalities; symptomology in these cases include respiratory depression, somnolence or unconsciousness, cyanosis and pulmonary/cerebral edema. These effects are common to other opioid receptor agonists, such as oxymorphone and methadone.

Acetyl fentanyl

Acetyl fentanyl, (*N*-phenyl-*N*-[1-(2-phenethyl)piperidin-4-yl] acetamide), a fentanyl analog in which the *N*-propionyl moiety is replaced with an acetyl moiety (Figure 1), rose to prominence in 2013 as the causal agent in 14 overdose deaths in Rhode Island over 3 months (211). The analgesic activity of acetyl fentanyl is estimated to be ~16 times more potent than that of morphine and 1/3 the potency of fentanyl (212). Additional states reported acetyl fentanyl fatalities in 2013 and 2014, and continues to be detected in postmortem toxicology cases in USA (213) and Russia (214).

Acetyl fentanyl has been found alone and in combination with fentanyl and other fentanyl analogues in drug intoxications and fatalities. In Florida, peripheral blood acetyl fentanyl concentrations reported in four cases were 31–600 ng/mL when acetyl fentanyl was the only drug present, and 6–12 ng/mL when fentanyl concentrations were 15–21 ng/mL (n = 3) (215). Additional acetyl fentanyl case reports with case histories and biological confirmations are listed in Table VII (185–189).

Although acetyl fentanyl was detected in USA in 2013, it took time before it emerged in Europe, which generally sees these substances first. Acetyl fentanyl was confirmed in a series of non-fatal intoxications presenting to the emergency department in Sweden between April and November 2015; serum concentrations (n = 7) ranged from 0.6 to 51.6 ng/mL (184). Naloxone was successfully administered in most cases, further substantiating acetyl fentanyl as an opioid agonist. In Europe, acetyl fentanyl was confirmed in one death in 2013, two in 2014 and 29 in 2015; in 19 of the deaths, acetyl fentanyl was the cause of or contributor to death (216). Acetyl fentanyl was banned as a Chinese export in October 2015, along with butyryl fentanyl, but it is too early to assess the international impact of the ban on the recreational drug market.

Butyryl fentanyl (Butyrfentanyl)

Butyryl fentanyl (*N*-[1-(2-phenethyl)-4-piperidinyl]-*N*-phenylbutramide), another fentanyl derivative with an *N*-propionyl group replacing the acyl group. Preclinical evidence suggests that butyryl fentanyl is seven times more potent than morphine and ~10 times less potent than fentanyl (212). Butyryl fentanyl first appeared in the illicit drug supply in USA in 2014. It had been first reported by the Early Warning System operated by the EMCDDA and Europol from seizures in Poland in the summer of 2013, before its appearance in the US. Sweden reported its first seizures in April 2014; two intoxications presenting to the emergency department had serum concentrations of 0.9 and 0.6 ng/mL, with concomitant fentanyl concentrations of 4.3 and 10.2 ng/mL (190). An additional US butyryl fentanyl intoxication is included in Table VII, as well as fatalities (191–193, 217). Butyryl fentanyl may undergo postmortem redistribution, based on analysis of butyryl fentanyl in multiple specimens, including paired cardiac and peripheral blood samples (191–193).

AH-7921

AH-7921 (3,4-dichloro-*N*-(1(dimethylamino)cyclohexylmethyl) benzamide) is a structurally atypical opioid analgesic patented by Allen and Hanburys LTD in 1976, although it never was marketed. Preclinical studies indicated that AH-7921 produced agonist effects at the μ-opioid receptor, with ~80% of the potency of morphine (218). AH-7921 abuse was reported in Europe, leading to a series of severe toxicity cases as well as 16 reported deaths between December 2012 and September 2013 (219). Reported blood concentrations ranged from 31–1,449 ng/mL in European fatalities involving AH-7921 (11, 159, 220). AH-7921 subsequently disappeared from Sweden's illicit drug market once it was banned in August 2013. There are only a few reports of AH-7921 intake in the US, although it was chemically confirmed and reported in NFLIS data. These fatalities are listed in Table VII (194, 195).

MT-45

MT-45 (1-cyclohexyl-4-(1,2-diphenylethyl)piperazine) (Figure 1) is a *N*,*N*′-disubstituted piperazine, structurally unrelated to morphine or other opioid receptor agonists, and was sold illicitly as an AH-7921 alternative online. It was originally investigated in the 1970s by the Japanese Dainippon Pharmaceutical Company as an analgesic (221). Structure activity relationship studies suggest that the nitrogen at the 4-position plays a key role in determining its opioid effects, and preclinical testing indicated that MT-45 may be more potent than morphine; however, there are no human studies (222–225).

Sweden has reported the majority of published MT-45 exposures including 28 fatal and 18 non-fatal intoxications between November 2013 and July 2014, following Sweden's ban of AH-7921(226, 227). All 28 fatal and 12 of 18 non-fatal intoxications were analytically confirmed. In 19 of 28 deaths, MT-45 was reported as the cause or contributor to death. MT-45 blood concentrations in the 28 reported deaths ranged from 8.3–1,989 ng/mL; in the two cases where MT-45 was the sole substance, concentrations were 156 (individual jumped off a building) and 802 ng/mL (individual found deceased at home). Of the 12 confirmed non-fatal intoxications from Sweden, quantitative blood results were available for two cases, 344 μg/mL and 62 ng/mL, with flubromazolam and THC identified in the second case. In another series of nine non-fatal Swedish intoxications (all males, ages 17–32 years), MT-45 was detected in blood at 6–157 ng/mL; in addition to typical opioid adverse events such as unconsciousness and respiratory depression, three patients reported ototoxicity (228).

MT-45 has been rarely reported in USA; the US Department of Homeland Security through Immigration and Homeland Security Investigations reported the deaths of two New Yorkers from MT-45 and ethanol in August of 2013 (229). A single fatality from Vermont is described in Table VII (196).

U-47700

Although AH-7921 and MT-45 were not popular with US drug users seeking a novel opioid high, U-47700 (*trans*-3,4-dichloro-*N*-(2-(dimethylamino)cyclohexyl)-*N*-methylbenzamide), another pirated pharmaceutical, appeared in 2015 (230). U-47700 (Figure 1) is an opioid analgesic structurally related to AH-7921 developed by Upjohn in the 1970s. It is a selective μ-opioid receptor agonist, and in preclinical models has ~7.5 times the potency of morphine (231, 232).

U-47700 was identified in adverse events in 2015 and its prevalence rose throughout 2016. This includes non-fatal intoxications and fatalities, described in Table VII (197, 199, 201–204). U-47700 concentrations in these cases varied widely, ranging from 7.6 to 1,460 ng/mL. U-47700 was confirmed in blood from 16 fatalities across USA in 2015–2016, with blood concentrations of 17–490 ng/mL, (253 ± 150 and 257, mean and median, respectively) often with other drugs, including five cases with furanyl fentanyl (233).

Furanyl fentanyl

Furanyl fentanyl (*N*-(1-(2-phenylethyl)-4-piperidinyl)-*N*-phenylfuran-2-carboxamide) was synthesized and patented in 1986, but did not appear on the illicit market until late 2015. It was confirmed in eight cases across the USA, with blood concentrations ranged from 2.5 to 76 ng/mL (26 ± 28 and 12.9, mean and median, respectively) (233). Two 2015 Swedish non-fatal drug intoxications are detailed in Table VII (184). A case series from Canada in the summer of 2016 was the result of a batch of crack cocaine from one dealer that was contaminated with furanyl fentanyl, further reinforcing the dangers posed to illicit drug users who are unaware of what they are buying (234).

Other novel synthetic opioid agonists, analogs and derivatives

There are sporadic reports of other fentanyl analogs, including beta-hydroxythiofentanyl, fluoro-fentanyl isomers, carfentanil, a resurgence of 3-methyl fentanyl and others. Additional case reports of 4-methoxybutyryl fentanyl, 4-fluorobutyryl fentanyl and ocfentanil are included in Table VII (184, 190, 205, 206, 235). The breadth of fentanyl derivatives continues to expand, challenging the global community.

Mitragynine

Mitragynine (Figure 1) is chemically dissimilar from all other opioids, as it is a naturally occurring alkaloid from the plant *Mitragyna specios*. Mitragynine has conventionally been used in folk medicine, but has found secondary applications for recreational purposes, making its current use novel. This plant, commonly referred to as "Kratom" in Thailand and as "Biak-Biak" in Malaysia, is native to Southeast Asia and traditionally used as an herbal remedy for fatigue or pain. Mitragynine is also popular as a natural substance for the treatment of opium withdrawal and pain. Mitragynine is considered to be the major constituent in the plant, although there are ~40 different alkaloids present, including 7-hydroxy mitragynine. Mitragynine and 7-hydroxy mitragynine are μ-receptor agonists. Kratom has dose-dependent pharmacological effects, and has stimulant-like effects at low doses and an opioid-like sedative effect at high doses. In a mitragynine pharmacokinetic study, ten chronic Kratom users were dosed with 104, 166 and 192 g/mL Kratom teas over 7 days, achieving plasma mitragynine concentrations up to 191 ng/mL (236).

Kratom is easily purchased over the internet, alongside other NPS, as teas, pills, liquids and herbal blends for smoking. It is unknown how many individuals are attempting to self-medicate with Kratom versus abuse of Kratom for either the opioid- or stimulant-type effects. Texas poison control centers reported Kratom exposures from 2009 to 2013, with half in 2013; illustrating that Kratom is becoming an increasing cause of concern for USA (237). Clinical symptoms following use included tachycardia, hypertension, agitation, nausea, vomiting, tremor, diaphoresis, drowsiness, hallucinations, mydriasis, dyspnea, bradycardia, abdominal pain and slurred speech. Although Kratom is used to manage pain and opioid withdrawal, it also is potentially addictive. A 37-year-old woman with no previous history of substance abuse treatment was admitted to an inpatient treatment

facility for addiction to Kratom; she was attempting to reduce Kratom intake she took to treat pain from a recent surgery, and began to experience cravings as well as other significant withdrawal symptoms (severe abdominal cramps, sweats, blurred vision, nausea, vomiting and diarrhea) (238). The withdrawal symptoms required pharmaceutical management. Although marketed as a non-addictive, herbal remedy, mitragynine is the source of many adverse events and deaths, which are reported in Table VII (207–209).

Discussion

In 2013, novel opioid agonists became the next wave of the opioid epidemic. These substances appear in greater numbers in toxicology casework, but frequently are missed, due to concomitant fentanyl heroin, or other opioid use. Many times, these NPS are not detected unless specialized testing is ordered. Often the only clue pointing towards a novel opioid agonist is drug confiscated at the scene. The only other clue pointing towards a fentanyl derivative may be a positive fentanyl immunoassay screen and negative confirmation, as many analogs cross-react. However, the atypical opioid analgesics such as AH-7921, MT-45 and U-47700, are not structurally similar and do not cross-react. Further complicating these cases is that many involve other substances. Polysubstance abuse complicates all toxicology cases, but is particularly difficult in NPS cases, because it is difficult to assess the impact of new drugs compared to more traditional substances, as there are few research data for novel opioid agonists. These novel opioid agonists pose the same public health dangers as other NPS classes including ease of accessibility over the internet, new drug introductions following scheduling, requirement for specialized toxicology testing, lack of certified reference material, limited knowledge of effects in humans, and misrepresentation to users. However, in addition to these challenges, there is also the added concern that these novel opioid agonists are found in the routine illicit heroin and fentanyl drug supply, increasing the pool of potential victims.

Summary and Conclusions

This review reflects the fact that NPS markets continue to evolve rapidly. Among the current trends is the continued and sustained turnover of synthetic cannabinoid agonists and evidence of their toxicity, including increased identification in hospitalizations and deaths. Laboratories continue to struggle significantly with the synthetic cannabinoid drug class. The diversity of chemical structures that are possible with modifications, substitutions, halogenation and alkyl homolog variations that retain receptor binding activity and, in many cases, functional activity, speak to the complexity of the class. The prevalence of reported adverse events compared to those associated with cannabis, a far more widely used drug, suggest that the pharmacology of these compounds is not fully understood.

The turnover of synthetic cathinones in stimulant drug markets has resulted in the decline of alpha-PVP and its replacement with other synthetic cathinones such as ethylone, butylone, dibutylone and, most recently, *N*-ethyl pentylone. Quickly identifying these trends and providing analytical data to support toxicology testing will require laboratories to frequently update mass spectral databases, to include mass, retention time and fragment information. Since the onset of effects can be acute and often unwitnessed, documentation of drug use history, scene investigation and complete screening and confirmatory testing will be required to provide evidence as to which substances are related to adverse events, up to and including death.

Novel hallucinogens represent a diverse chemical class. Adverse effects differ between subclasses based on their chemical structure and pharmacological profiles. While all novel hallucinogens are associated with cardiac effects, such as tachycardia, some novel hallucinogens are linked to more specific adverse behavioral and physiological effects such as agitation, aggression, bodily harm and excited delirium. Due to this variety of subclasses involved and their potency, there is an increasing need for more standardized laboratory testing practices to improve the detection of novel hallucinogens in fatality and DUID investigations.

The appearance of designer, non-prescription benzodiazepines is of concern due to their potential for proliferation and interaction with other CNS depressant drugs and alcohol. Prescription benzodiazepines are rarely responsible for death when taken alone, even at significantly high doses; however, the greatest toxicity is their interaction with alcohol, which is a common pattern of use. The fact that these drugs are being created for recreational drug markets significantly increases the risk that they will contribute to drug-related deaths in 2017. Lack of awareness about designer benzodiazepines in the toxicology and emergency medicine communities may result in less success in identifying intoxications. Some of these drugs cross-react on benzodiazepine ELISA kits but are often not in the scope of confirmatory assays, creating the risk for increasing rates of unconfirmed immunoassay positive results. The designer benzodiazepines that do not cross-react on ELISA will be missed during immunoassay-based drug screening protocols, such as those commonly used in hospital urine drug screens.

From a public health and safety point of view, one major development in the last year (and probably not completely reflected in the published literature as of December 2016) was the rise of designer opioids and the dramatic increase in adverse events associated, including death, across the United States. This drug class has proven to be the most severe in relation to adverse events and the frequency of events, as this trend is likely to continue. Designer opioids of particular note are U-47700, furanyl fentanyl and butyryl fentanyl, although these compounds are already waning in frequency of detection. By the end of 2016, the authors' laboratory encountered and reported over 100 carfentanil related results in death investigation cases, suggesting that this potent designer opioid will be a significant drug of concern in 2017, though literature reports are currently rare.

The identification of a new substance in NPS markets often comes about through an incident of mass-poisoning or a series of deaths in a specific location. These events are tied by case history, scene investigation and circumstances; but for the reasons considered above, the initial toxicological testing is frequently negative. Routine approaches to analytical toxicology, based on a tiered approach of immunoassay coupled with targeted gas or liquid chromatography mass spectrometry, are now more likely to fail to find the causative agent because the defined scope often does not include the most current NPS. During non-targeted screening, the presence of a substance may be identified, but if certain information is not present in in-house databases, identification may not be positive and therefore not reported. With some classes of drugs, such as the typically neutral synthetic cannabinoids, widely used routine basic extraction chemistries are not targeting and isolating these compounds, so the extracts themselves may not recover a certain NPS that is present.

For all these reasons, traditional approaches to solving toxic incidents or deaths derived from common therapeutic or abused agents are not adequate for the challenges of NPS markets. This is driving

laboratories towards high-resolution mass spectrometry techniques (i.e., time-of-flight mass spectrometry) and more non-targeted analytical approaches, adding cost and complexity to analysis for the detection of high risk low frequency intoxication events. While these approaches are increasingly feasible for some forensic toxicology laboratories, it is rare that more comprehensive testing is ever performed to identify the causative agent in clinical intoxications, since treatment is supportive and based on symptomology. Testing results for the non-traditional drugs (i.e., beyond traditional opiates, cocaine, amphetamines and benzodiazepines) are not used in patient care, and therefore the procedures are not reimbursable by insurance companies. Delays in identifying the presence of the intoxicating agent have significant consequences for public health and public safety.

Challenges arise for forensic toxicologists regarding interpretation of NPS results in general (239), and even more so when multiple NPS and drugs of abuse are present. Co-ingestion of NPS with other NPS or common drugs of abuse is unstudied and therefore interpretation is widely speculative, leading to difficulties in formulating opinions based on multi-drug toxicity and effects. What can be surmised is based off basic knowledge of pharmacology, not necessarily receptor efficacy or binding affinity profiles, which are typically lacking in regard to these novel substances. Combinations involving benzodiazepines and opioids are commonly encountered in forensic toxicology and are understood to be additive in nature, so it is likely that designer or novel versions of these analytes are likely to be at least additive as well when encountered together. Designer opioids are often found in combination with fentanyl and/or other designer opioids, which would likely lead to a greater risk of overdose and death due to variability in potency and formulations. As seen in Tables III–VII, drug results can vary in number and diversity, as well as concentration, making the correlation between co-ingestion and adverse events complex and unsubstantiated.

Recommendations

The United States should develop a national monitoring program to provide real-time clinical and forensic toxicology data to medical, forensic and treatment communities on emerging drugs and their known toxidromes and side effect profiles. Such a system will need to be monitored, managed and curated to ensure that the data are evidence-based, the data are comprehensive, and the substances have been confirmed analytically.

We need to implement toxicological testing of samples from individuals reporting to emergency departments and hospitals following adverse events and ingestion of NPS. This would contribute to our early identification of NPS by being able to flag compounds of concern among drug-using communities. These findings would help educate and warn user populations of dangerous new products or substances before they start causing adverse effects and fatalities.

Finally, toxicology laboratories can prepare themselves for their first encounters with NPS by a variety of means. These include: keeping a dialog with local forensic chemistry laboratories to improve awareness of what substances are being seized and detected in the street drug supply, monitoring drug trends from domestic and international organizations and governments, reviewing data from poison centers, reviewing additions to the federal drug schedules, reviewing available standards offered by standard reference material suppliers, and reviewing activity and traffic on drug user internet forums, among other approaches. This preparedness approach is strongly recommended as a means of increasing early detection of new drugs, including NPS, in forensic and clinical populations.

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