THERAPEUTIC DRUG MANAGEMENT AND TOXICOLOGY DIVISION NEWS
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Therapeutics & Toxins News

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In This Issue:

Designer Drugs – A Brief Overview

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'Designer drugs', also known as novel psychoactive substance, (or NPS), is the overarching term used to describe various groups of synthetic psychoactive compounds created solely for recreational use.(1)

Specifically, designer drugs refer to substances that are typically synthesized based on results from legitimate pharmaceutical research, (i.e., medical research publications and scientific patents), to provide the desired psychoactive and/or physiological effects.(1-3)

Typically, these chemical compounds are designed and manufactured to exploit loopholes in existing laws on controlled substances, thus circumventing legal regulations. For example, the package labels may be intentionally inaccurate to appear as a legal substance, while also listing that the content is "not for consumption". As the result, the end-users are able to purchase and abuse these illicit substances with greater ease – thus coining the term "legal highs" as an alternative name for NPS.(1, 4-6)

Several classes of designer drugs have been described extensively in the literature, including stimulants, cannabinoids and hallucinogens (Table 1). A short overview of each of these categories will be provided in this article.

Table 1. Examples of synthetic cannabinoids, synthetic hallucinogens and synthetic stimulants (References for the table: (7-12))

Class	Examples of drugs	Street names	Additional information
Cannabinoid	Naphthoyl derivatives • JWH-018 • JWH-073 Cyclohexylphenol • CP55,940 Dibenzopyrane derivative • HU-210 Carboxamide Indazole derivatives • AB-FUBINACA	• Spice • Cloud 9 • Herbal incense • K2 • Mojo	• Designed to mimic marijuana – specifically, the psychoactive component of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC) – and bind to the same cannabinoid receptor in the brain
Hallucinogen	NBOMe • 25I-NBOMe • 25C-NBOMe • 25B-NBOMe	25I-NBOMe • 25-I • BOM-Cl • BOME • Holland Firm • Legal Acid • N-Bomb • N-boom • Smiles • Solaris	• Substances in the NBOMe group are phenethylamine derivatives of the 2C class of hallucinogens • 25I-NBOMe is one of the more common/popular drugs within the group which has emerged as a legal substitute for lysergic acid diethylamide (LSD)
Stimulant	Cocaine-like cathinones • 3,4-methylenedioxypyrovalerone (MDPV) • Pyrovalerone MDMA-like cathinones • Mephedrone • Methylone Methamphetamine and amphetamine-like cathinones • Cathinones/Methcathinone • α-pyrrolidinopentiophenone (α-PVP)	• Bath Salts MDPV • Ivory wave • Vanilla Skye • Energy 1 Mephedrone • Meow-meow • M-cat α-PVP • Flakka • Gravel	• Bath salts are mostly derivatives of cathinones • MDPV is thought to be the primary contributor for the fatal adverse effects of bath salts due to its structure, making it a lipophilic compound that can easily cross the blood brain barrier

Synthetic cannabinoids are designed to emulate true cannabinoid and provide the similar "happy" and "relaxed" feelings. However, adverse effects SC intoxication can include nausea, weakness, tachycardia and hypertension, as well as irritability and anxiety.(13)

Furthermore, the synthetic cannabinoids are generally considered to be more potent than marijuana due to stronger binding affinity (relative to Δ^9-THC) to the cannabinoid receptors, as well as the drugs ability for binding to additional receptors that Δ^9-THC doesn't normally interact with. (8)

The synthetic cannabinoid family is both large and diverse. It has been estimated that there are over 120 synthetic cannabinoids and the list is continuing to grow.(10) This list includes a variety of compounds, including those that can be further classified as alkoyl, benzoyl, benzimidazole, carboxamide, carboxamide indazole, carboxylate, carboxylate indazole, indazole, naphthoyl, naphthoyl pyrroles, naphthylmethyl, naphthylmethylindenes, phenylacetyl, piperazoyl, pyrrole, and thiazolyl derivatives. The specific examples within each group have been summarized elsewhere.(10)

Several methods have been developed for the detection of synthetic cannabinoids. Immunoassays are commonly used for drug screening purposes to identify presumptive positive samples. Although immunoassays are available for the relatively more common families of synthetic cannabinoid, e.g., JWH-018, these assays often lack cross-reactivity towards the newly-marketed, related synthetic cannabinoids.(14) As such, the number of synthetic cannabinoids immunoassays can detect is often considered low and outdated in the field of designer drugs.(14)

Theoretically, mass-spectrometry (MS) based methods may be better able to keep up with the emerging designer drug market. This is because new MS methods can be more readily developed to target new analytes, as soon as the structures and/or spectra of the compounds are identified via analysis of human liver microsome and hepatocytes using instruments such as the high-resolution mass spectrometers. (15, 16)

For example, the study from Scheidweiler et al. demonstrated the utility of liquid chromatography-quantitative time of flight (LC-QTOF) in the simultaneous identification of 47 common synthetic cannabinoid metabolites (derived from compounds from 21 synthetic cannabinoid families) in urine.(16) This particular method also utilized the Sequential Windowed Acquisition of All Theoretical Fragment Ion Mass Spectra (SWATH-MS), which is a non-targeted data acquisition method that has been utilized in other systemic toxicological studies.(17) Analysis of synthetic cannabinoid in serum and whole blood samples using Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) has also been demonstrated by the works of Kneisel, Knittel and others.(18, 19) Ultra High Performance Supercritical Fluid Chromatography (UHPSFC) has also demonstrated its

potential in providing better separation of synthetic cannabinoids, particularly positional isomers and diastereomers.(18, 19)

Synthetic Hallucinogen

Hallucinogens, by definition, are drugs that can induce hallucinations or other psychedelic effects. A widely known, prototypical hallucinogen is lysergic acid diethylamide (LSD). A group of designer drugs called NBOMe, sometimes referred to as 25x-NBOMe, consist of various phenethylamine derivatives of the 2C class of hallucinogens. Some examples of NBOMe include compounds such as 25I-NBOMe, 25C-NBOMe, and 25B-NBOMe.(7, 20)

More notably, 25I-NBOMe, or "N-bomb", is one of the N-benzyl phenethylamines which has emerged as a common replacement for LSD.(21) The hallucinogenic effects of 25I-NBOMe is in part contributed by its N-2-methoxybenzyl group, which increases its binding affinity to the serotonergic 5-HT2A receptors.(20) This results in a higher potency compared to the classic hallucinogen 2C-I (or 2,5-dimethoxy-4-iodophenethylamine).(7) The symptoms associated with serotonergic drugs like hallucinogens include hyperthermia, seizures, tachycardia, depersonalization, as well as visual and auditory hallucinations.(20, 21)

While there are various routes of administration of 25I-NBOMe, e.g., nasal, sublingual, buccal (via blotting paper), oral, intravenous or intramuscular injection, rectal, etc., the most commonly used method is similar to that of LSD, which is commonly done via the buccal and sublingual routes.(7) Specifically, "blotter papers" are often used, which are essentially paper tabs that have been loaded with the designer drug.

Although 2C designer drugs have been around since the 1970's, compounds such as 25I-NBOMe are still considered relatively new.(22) Studies that examined the utility and cross-reactivity of rapid drug screening immunoassays have largely demonstrated that, while certain assays are able to pick up specific compounds within the 2C series of hallucinogens (23), immunoassays can have difficulty detecting the relatively newer 2C class compounds, such as 25-I-NBOMe, particularly at lower drug concentrations.(22, 23)

Several studies in the recent years have demonstrated the utility mass spectrometry based methods in the screening and detection of synthetic hallucinogens. The study from Poklis et al. demonstrated the use of Direct Analysis in Real Time AccuTOF™ for screening of 2C class hallucinogens on blotter paper.(24) As well, they were able to achieve quantification and confirmation of specific compounds, e.g., 25I-NBOMe, 25C-NBOMe or 25B-NBOMe, using high-performance liquid chromatography (HPLC) triple quadrupole mass spectrometry.(24) Similarly, mass spectrometry that involves an upstream ultra-high (or high-performance) liquid chromatography have been shown to be able to detect 25I-NBOMe, as well as other NBOMe class of drugs (e.g., 25B-, 25C-, 25D-, 25H-, 25I- and 25T2-

NBOMe), in both ante- and post-mortem specimens, including blood, urine, and other body fluids.(25, 26) More recently, study from Caspar et al. have also demonstrated the potential of liquid chromatography-high resolution tandem mass spectrometry (LC-HR-MS/MS), albeit in animal models, in the detection of sixty-eight 25I-NBOMe metabolites of in urine samples.(27)

Synthetic Stimulants

Stimulants refer to compounds that can increase one's energy and ability to focus, improve one's mood and wakefulness, as well as decrease one's appetite.(7) Some examples of commonly known stimulants include cocaine, amphetamines, methylphenidate (Ritalin), caffeine, and nicotine. In terms of designer drugs, synthetic stimulants are often derivatives of cathinone, which is the primary active ingredient (a monoamine alkaloid) found in the plant *Catha edulis* (khat), a known herbal stimulant native to East Africa and the Arabian Peninsula.(7, 21)

In general, stimulants carry out their function through several mechanisms, including the alternation of dopamine and noradrenalin regulation (e.g. pyrovalerone) and induction of monoamine secretion (e.g., amphetamines).(20) Some of the side effects of stimulants and cathinones include headache, sweating, palpitation, tachycardia, nausea, chest pain, as well as psychosis, agitation, and possible skin discolorations.(7)

One of the synthetic stimulants which have been reported in a number of overdose cases over the last 5 years or so is "bath salts", which are mostly derivatives of cathinones.(1, 7) Interestingly, bath salts products tend to contain a mixture of different cathinones; however, MDPV has been reported as the predominant ingredient found in urine and blood samples of victims from bath salts overdose cases in the United States.(1) It is thought that MDPV is the primary contributor for the fatal adverse effects of bath salts in part due to the structure, which contains a pyrrolidine ring and a tertiary amino group, thus making it more lipophilic compound relative to other cathinones, allowing it to cross the blood brain barrier more easily.(28)

Given that cathinone molecules can be chemically modified at 9 different positions, there is a huge variety of derivatives.(9) This is troublesome in terms of both the screening and detection of these designer drugs, as well as understanding the toxicological effects.(9) Similar to the case of hallucinogens, there are currently several immunoassays available for synthetic stimulants.(23) However, the number of compounds these immunoassays can detect, given the ever-expanding class of synthetic cathinones, is still lacking.

In the last several years, techniques such as ion-mobility spectrometry mass spectrometry (IMS-MS) have been utilized in attempt to analyze synthetic cathinones.(28, 29) As well, other mass-spectrometry based methods, including full-scan high-resolution mass spectrometry (HRMS), gas chromatography mass spectrometry (GC-MS), and liquid chromatography tandem mass spectrometry (LC-MS/MS) are gaining traction as alternative

means to unambiguously identify and quantify synthetic stimulants, amongst other designer drugs.(9, 30-32) For instance, in the study by Ambach et al., LC-MS/MS was able to detect and quantify 56 novel psychoactive substances in blood and urine, including amphetamine derivatives and cathinones, in a run time of just 20 minutes.(30) More recently, the study by Lendoiro et al. have also demonstrated the possibility of applying LC-MS/MS to analyze hair for amphetamine-type stimulants, including selected synthetic cathinones such as methylone, methedrone, and MDPV. (33)

Summary

Given the emerging market of designer drugs and the consistently-expanding list of new compounds, it is clear that accurate detection and quantitation will be a great challenge for the clinicians and laboratorians. While existing rapid drug screening immunoassays do provide a certain level of support and guidance for the clinicians, it appears that mass-spectrometry-based methods may be able to better keep up with the ever-changing field of designer drugs. As described earlier, MS-based methods can potentially allow a more rapidly development of assays for new analytes, as soon as the structures and/or spectra of the newly identified compound(s) becomes readily available.

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Musings from the Chair,

Section Activities in AACC National Meeting (Philadelphia): July 31 to August 5, 2016

I'm looking forward to seeing you all at this year's annual AACC meeting in Philadelphia. We'll becoming in right after the Democratic National Convention so if you get there early you may even catch sight of the Hillary. As usual, we will be holding our annual membership meeting and luncheon on Monday August 1st from noon until 2:00 at the Marriott Philadelphia Downtown in the Independence Ballroom Salon III. This year the meeting will feature our awards presentations for the best abstracts and the Young Investigator Award. We will also be announcing the winners of our recent election and be treated to a lecture by Dr. Anthony Burch, Ph.D., Professor & Director of Chemistry/Toxicology, UCLA Medical Center. All in all we hope it will be an interesting program to say nothing about catching up with old friends.

Again this year we have been asked to supply a leader for the poster walk on Wednesday August 3rd from 12:30 till 1:00. Unfortunately, no one has volunteered to be the leader this year. So if you are interested please let me know ASAP. This would be the fourth year in a row that we have participated in the poster walks. The poster walks can be a great way to learn the latest techniques, see what your colleagues are up to, and to make new acquaintances. I urge you all to volunteer and attend.

Finally, this is a time of much change for the AACC. By now you are all aware of the sweeping changes taking place in the governance structure of our organization. There are many changes involving the Divisions and I urge you to become familiar with the proposals and to vote in the bylaws change election to be held later this year.

That's all for now. Hope to see you in Philly!

Jim

Upcoming Conferences

AACC 2016
July 31-Aug 4
Philadelphia, PA

ASCLS
Aug 3-6
Philadelphia, PA

Northeast Lab Conference
Oct 18-20
Portland, ME

AMP 2016
November 10-12
Charlotte, NC

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