

TITLE: Synthetic Drugs: Cathinones and Cannabinoids

PRESENTER: Steven W. Cotten, PhD

Slide 1

Hello, my name is Steven Cotten. I am an assistant Professor in Pathology and Associate Director of Chemistry and Toxicology at the Ohio State University Wexner Medical Center. Welcome to this Pearl of Laboratory Medicine on “Synthetic Drugs: Cathinones and Cannabinoids.”

Slide 2:

In this Pearl, we will review two distinct illicit drug classes: cathinone derivatives and synthetic cannabinoids. Beginning around 2006, both cathinones and synthetic cannabinoids made national and international headlines for their rapid emergence as “legal” highs. Neither class of drugs was formally marketed for human consumption. Instead, cathinones were promoted as “bath salts” and synthetic cannabinoids were sold under the names K2 and SPICE.

For cathinones, we will review the chemistry, legal implications, association with excited delirium, and laboratory detection. For synthetic cannabinoids, we will review their research origins, chemical diversity, effects, and laboratory detection.

Slide 3:

Cathinone is a natural product from *Catha edulis*, a plant native to the Horn of Africa and Arabian Peninsula, also commonly known as Khat. Traditional consumption of Khat involves chewing the leaves, which results in mild stimulant and euphoric effects. Cathinones share a high degree of structural similarity to other amphetamines. The biological activity is also similar to amphetamines, increasing the concentration of neurotransmitters through inhibition of serotonin, dopamine, epinephrine, and norepinephrine reuptake.

Structurally, the molecule has four main functional groups: an aromatic ring, a ketone, an alkyl side chain, and an amine group. Although cathinones have a high degree of structural similarity to amphetamines, they are largely undetectable in conventional amphetamine immunoassays. As mentioned earlier, derivatized versions of cathinones were sold under the guise of bath salts, incense, and iPhone cleaner. Numerous overdoses and deaths have resulted from the abuse of cathinones. The majority of the identified drugs to date are analogs of methcathinone, a methylated derivative of cathinone.

Let’s explore some of the different derivatives of methcathinone that have been identified.

Slide 4:

If we begin with the basic structure of methcathinone, shown in the center, different substitutions can be made from three of the functional groups. Substitutions on the aromatic ring (shown at the right) can include, methyl, methoxy, and methylene dioxy groups. In the case of methylenone, the structure is a close analog of the more commonly abused drug MDMA or ecstasy, only differing by the presence of the beta-ketone. Amine substitutions (shown at the top) can include ethyl groups off the amine or 5-membered pyrrolidine rings. Identified alkyl substitutions can include 2 or 3 carbon chains in the case of buphedrone or pentedrone. Finally, substitutions at all three groups give rise to structurally novel cathinone derivatives such as MDPV. It should be noted that these are only representatives of the myriad of compounds that have been identified.

Slide 5:

The potential for such a wide variety of substitutions has created a cat and mouse game for both regulatory agencies, such as the DEA, and clinical and forensic laboratories. From 2010 through 2013, there were 9,000 reports from state and local forensic laboratories that identified cathinone derivatives in seized samples, leading the DEA to classify mephedrone, MDPV, and methylenone as Schedule I substances in the fall of 2011. Five more classes of synthetic cannabinoids and additional cathinones were subsequently added in 2012 when the Synthetic Drug Abuse Prevention Act was passed; and again two years later, 10 additional cathinones were classified as Schedule I. The continuous process of drug derivatization by underground manufacturers, identification by law enforcement, and subsequent updates in legislation by the government creates an unpredictable cycle of constantly changing drug policy.

Slide 6:

Much of the challenge with regulation comes from the Federal Analog Act of 1986. An analog was defined as any chemical that is substantially similar to a Schedule I-controlled substance and therefore, can be treated as such. The definition of substantially similar is not explicitly defined and two Supreme Court cases have illustrated different interpretations of the law. In *USA vs. Forbes*, the psychedelic tryptamine AET was found not to be similar to the controlled substances DMT and DET (and the closely related psilocybin). Alternatively, *USA vs. Washam* found that 1,4 butanediol, a compound that is converted to GHB *in vivo*, was similar and should be treated like a Schedule I substance.

In 2015, an amendment to the Synthetic Drug Abuse Prevention Act created the Controlled Substance Analog Committee. This interagency committee with personnel from the DEA, NIDA, CDC, and other agencies has the goal to determine similarity of potential compounds. Additionally, the Advisory Committee for the Evaluation of Controlled Substance Analogs was created to scientifically and objectively define criteria for drug similarity. Their website and mission statement can be found at www.druganalogs.org

Slide 7:

The effects and potency of substituted cathinones can be unpredictable and have often led to overdose and intoxication. In certain cases, a collection of symptoms called Excited Delirium Syndrome can be seen. These consist of altered mental status, combativeness, hyperthermia, metabolic acidosis, and "superhuman strength." All of these symptoms are consistent with a sympathomimetic amine activity.

Death may occur in extreme cases due to respiratory arrest or fatal cardiac arrhythmia. Altered mental status and confusion can arise from elevations in sympathomimetic neurotransmitters, especially dopamine. Due to hyperthermia, users may often be naked in an attempt to cool down. Rapid breathing accompanies metabolic acidosis as a means to remove the buildup of CO₂. Superhuman strength may result from excess epinephrine (adrenaline) in the system.

Slide 8:

Routine detection of substituted cathinones is not currently performed in most clinical labs. Despite structural and biological similarities, cathinones are not detected with conventional immunoassays for amphetamines. The majority of amphetamine assays have been designed to target d-amphetamine or methamphetamine and show no reactivity towards cathinones, even at supra-physiological concentrations. There are a limited number of specialized assays that target MDPV or mephedrone/methcathinone. Additionally, untargeted MS-TOF or library spectra-based screening could identify cathinone derivatives. MRM-based LC-MS/MS can also be used if commercial standards are available for the compounds of interest.

Let's shift gears now and talk about another class of synthetic drugs, the synthetic cannabinoids.

Slide 9:

Synthetic cannabinoids are a class of compounds with biological activity at the CB1 and CB2 receptors. Structurally they are unrelated to THC, but instead are chemical entities from legitimate research labs and major pharmaceutical companies studying pain and anti-obesity drugs. These compounds were openly sold under the names SPICE and K2 in the "grey" market of research chemicals.

The first two major classes were the JWH and HU/CP Series. JWH compounds were first synthesized (and named) by John W. Hoffman at Clemson University. Cannabinoid activity was first published in 1999 and JWH-018 was the first-generation compound to illustrate CB receptor binding. Raphael Mechoulam at Hebrew University synthesized the HU series. Pfizer also developed a similar compound in 1982.

Slide 10

If we look at the structures of some of the four earliest compounds, we can see they fall into two major structural classes. The JWH series overlays nicely with the WIN series and the HU series overlays well with the CP series.

Slide 11:

Much like substituted cathinones, there was a rapid evolution in the chemical diversity of synthetic cannabinoids beginning around 2010. Analysis of seized compounds identified fluorinated derivatives of the first-generation compounds followed by additional substitutions of the aminoalkylindoles of the JWH series. Interestingly, additional patented compounds from pharmaceutical companies began appearing. Now, patented research chemicals from GlaxoSmithKline, Abbott, Bristol Myers Squibb, and Pfizer have all been identified in seized material.

Slide 12:

The biological activity, potency, and toxicity are largely unknown for the synthetic cannabinoids. Generation 1 compounds were relatively benign with similar activity and potency to THC.

However, it's important to remember that much of the research is limited to *in vitro* receptor binding studies and animal models. Data is unavailable for 2nd, 3rd, and 4th generation compounds related to potency, toxicity, or long-term effects.

Recent case reports suggest that these newer synthetic cannabinoids show increased potential for adverse effects. Arrhythmias, seizures, hospitalization, and acute kidney injury requiring hemodialysis have all been reported with these novel compounds.

A recent case report identified a 4th generation compound responsible for 76 people presenting to the ED. Seven of those patients required intubation and admission to intensive care units for medical management.

Slide 13:

Synthetic cannabinoids cannot be detected with conventional THC immunoassays. There are a few commercially available immunoassays, but they cannot reasonably stay current based on the ever-changing compounds being produced and their unpredictable cross-reactivity. Metabolites in the urine are primarily hydroxylated and excreted as glucuronides, but the position of the hydroxyl group on the molecule is not necessarily predictable based on the structure of the compound.

Detection via mass spectrometry is a popular method for laboratories to assay for synthetic cannabinoids. Free spectral libraries are available from Cayman Chemicals and the Scientific Working Group for the Analysis of Seized Drugs. Commercial libraries are also available for purchase such as the Designer Drug Library by Rosner. This database currently contains 3,000 distinct synthetic cannabinoid spectra, but the relevant metabolites may not be present.

Additionally, users should look for frequent updates to these libraries to stay contemporary with newer synthesized compounds.

Slide 14:

To summarize, substituted cathinones share both structural and biological activity with other common drugs of abuse like amphetamine, methamphetamine, and MDMA. Their biological activity is complex but work by blocking the reuptake of select neurotransmitters. Laboratory detection can be achieved via specialized immunoassays or mass spectrometry.

Synthetic Cannabinoids have significant chemical diversity and biological activity is unpredictable. Their activity is distinctly different from THC with a higher frequency of adverse side effects. Many of the chemical entities are from research companies and very little is known about any potential long-term toxicity.

What's on the horizon for designer drugs? Ketamine/PCP derivatives appear to be another emerging class of compounds sold on the black market. Methoxetamine (MXE), a derivative of ketamine, has recently been identified in seized material and has been implicated in hospitalizations.

Slide 15: References

Slide 16: Disclosures

Slide 17: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on “Synthetic Drugs: Cathinones and Cannabinoids.”