Clinical Implications of Synthetic Cannabinoid and Synthetic Hallucinogen Abuse

Snehal Bhatt, MD
Assistant Professor, Psychiatry
Medical Director, Addiction and Substance Abuse Programs
University of New Mexico
IHS Center for Tele-Behavioral Excellence
EPIDEMIOLOGY- THE PREVALENCE OF SYNTHETIC DRUGS IS RISING
Emerging Drug Items Identified in U.S. NFLIS Forensic Labs: 2010-2012

Number of Unique Types of Synthetic Drugs Identified Nationally: NFLIS (2010-2012)

Past Year Drug Use by 12th Grade Students: MTF, 2012

Percentage of U.S. Students (Grades 9 to 12) Reporting Past Year Alcohol and Other Drug Use, 2012 (N=3,884)

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>57%</td>
</tr>
<tr>
<td>Marijuana</td>
<td>39%</td>
</tr>
<tr>
<td>Synthetic Marijuana</td>
<td>12%</td>
</tr>
<tr>
<td>Rx Pain Relievers</td>
<td>10%</td>
</tr>
<tr>
<td>Rx Stimulants</td>
<td>9%</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>8%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>7%</td>
</tr>
<tr>
<td>Inhalants</td>
<td>7%</td>
</tr>
<tr>
<td>OTC Cough Medicine</td>
<td>7%</td>
</tr>
<tr>
<td>Crack</td>
<td>4%</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>4%</td>
</tr>
<tr>
<td>Salvia</td>
<td>4%</td>
</tr>
<tr>
<td>Bath Salts</td>
<td>3%</td>
</tr>
</tbody>
</table>

"SPICE" [SYNTHETIC CANNABINOIDs]
Anandamide- Endogenous Cannabinoid

![Anandamide chemical structure](anandamide_structure.png)
Anandamide- Endogenous cannabinoid

- “Ananda” = Sanskrit word meaning bliss, happiness, joy
- Anandamide and receptor sites are present in all mammals
- Anandamide and receptor sites are also present in birds, amphibians, fish, sea urchins, leeches, mussels, and even the most primitive animal with a nerve network, the Hydra, where it is involved in the “feeding mechanism”
Endocannabinoids are important!

• MODULATE:
  • Learning and memory
  • Social recognition
  • Regulation of anxiety
  • Regulation of pain threshold
  • Regulation of appetite
  • Emotional relevance determination
  • Forgetting aversive memories
Major receptors

• CB1 Receptors - 1988
  – Hippocampus – Memory and Learning
  – Amygdala – Novelty, Emotion, Appetites
  – Basal Ganglia – Motor
  – Cerebellum – Real Time Coordination, Selective Attention and Time Sense
  – **Nucleus Accumbens - Reward Mechanism (Addiction)**
  – Cortex (Anterior > Posterior) – Frontal Lobe Executive Functions

• CB2 Receptors - 1993
  – Macrophages
  – Spleen, Intestines
Δ9-THC: Exogenous cannabinoid
Synthetic cannabis
Also called...

- Spice
- K2/K2Gold
- Tai Fun blackberry/vanilla/orange
- Exclusive original/mint/cherry
- Natures Organic cherry/strawberry
- Chill Zone
- Chill Out
- Sensation
- Chaos
- Zen
- Black Mamba
- Clover Spring
- Aztec fire
- Bombay Blue
- Blaze
- Yucatan Fire
- Mr. Smiley
- Krypton
- Moon Rocks
- Zohai
- Fake Weed
Synthetic cannabinoids

• “K2”
• “Spice”
• Sold at head shops and gas stations
• Initially marketed as legal natural herbs
• However, DEA reports show that it in fact contains synthetic cannabinoids not yet illegal and not detected in standard urine tests
• Essentially, it is a designer drug
Synthetic cannabinoids

• Many synthetic cannabinoids produced from the 1960s onwards to study cannabinoid receptors
• These are sprinkled onto dried herbs [inert] including: rose hips, marshmallow, red clover, lotus, wild dagga, skullcap, baybean, beach bean etc.
• The mixture is then smoked
History

• “Spice” initially marketed in 2004 in Europe by a now defunct company called The Psyche Deli, based in London
• Now, it refers to any such product
• Usually marketed as “herbal incense” or “herbal smoking blend”
• Came to US 2008-2010 once these were banned in Europe and Russia
Multiple “generations”

• FDA: fifth and sixth generation drugs are now available
• On average, a new substance may come out every 4-6 days!!!
• Urine tests only test for upto 17
• Makes it very difficult to control and test
• Most recent one, CRB-754, inhibits enzyme that breaks down endocannabinoids!
Pharmacology

• FULL agonists of CB-1 and CB-2 receptors [THC only a partial agonist]

• Stronger binding affinity

• HU-210: 100-800x more potent than THC

• CB47-497: 30x more potent than THC

• JWH-018: 5x more potent

• Usually quicker onset of action and shorter duration
Why popular

• Potency
• Difficulty in detection= attractive to athletes, military personnel etc.
• Ready availability
• Misperceptions of safety
<table>
<thead>
<tr>
<th>Self-rated effect</th>
<th>Mean (SD)</th>
<th>Dependent samples t-test with effect size (Cohen’s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Synthetic</td>
<td>Natural</td>
</tr>
<tr>
<td>Pleasurable effects when high</td>
<td>4.98 (2.49)</td>
<td>8.59 (1.70)</td>
</tr>
<tr>
<td>Increase in appetite</td>
<td>3.79 (2.59)</td>
<td>6.89 (2.35)</td>
</tr>
<tr>
<td>Sedation (sleepiness after use)</td>
<td>4.51 (2.57)</td>
<td>6.16 (2.05)</td>
</tr>
<tr>
<td>Value for money</td>
<td>4.76 (3.00)</td>
<td>6.72 (2.27)</td>
</tr>
<tr>
<td>Ability to function after use</td>
<td>5.47 (2.76)</td>
<td>6.85 (2.34)</td>
</tr>
<tr>
<td>Impairment in memory</td>
<td>4.26 (2.78)</td>
<td>4.59 (2.42)</td>
</tr>
<tr>
<td>Addictiveness</td>
<td>2.62 (2.51)</td>
<td>2.97 (2.42)</td>
</tr>
<tr>
<td>Consistency of product</td>
<td>5.93 (3.17)</td>
<td>6.35 (2.36)</td>
</tr>
<tr>
<td>Hangover effects</td>
<td>3.49 (2.80)</td>
<td>2.79 (2.31)</td>
</tr>
<tr>
<td>Paranoia</td>
<td>4.75 (3.11)</td>
<td>3.89 (2.43)</td>
</tr>
<tr>
<td>Harmful effects on lungs</td>
<td>5.79 (2.85)</td>
<td>4.19 (2.35)</td>
</tr>
<tr>
<td>Negative effects when high</td>
<td>4.80 (2.89)</td>
<td>2.80 (2.00)</td>
</tr>
</tbody>
</table>
Characterization of exposures

- Hoyte et al. [2010]
- All -9-tetrahydrocannabinol homolog exposures reported to the National Poison Data System between January 1, 2010, and October 1, 2010, were extracted
- 1,898 exposures
- Tachycardia 37.7%
- 52 seizures [3.8%]; 2 cases of status epilepticus
- 78.4% effects lasted < 8 hours
- 92.9% non-life-threatening
- The most common therapeutic intervention was intravenous fluids [ 
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N=1,353 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>541 (40)</td>
</tr>
<tr>
<td>Agitation/irritability</td>
<td>317 (23.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>207 (15.3)</td>
</tr>
<tr>
<td>Drowsiness/lethargy</td>
<td>183 (13.5)</td>
</tr>
<tr>
<td>Confusion</td>
<td>164 (12)</td>
</tr>
<tr>
<td>Nausea</td>
<td>139 (10)</td>
</tr>
<tr>
<td>Hallucination/delusion</td>
<td>127 (9.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>110 (8.1)</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>99 (7.3)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>64 (4.7)</td>
</tr>
</tbody>
</table>
Key differences from marijuana

- Significant more irritability/agitation
- Seizures [epileptogenic agents such as \(O\) desmethyltramadol, an active metabolite of tramadol, found in herbal formulations]
Reports of kidney damage

- Sixteen cases of kidney damage reported by CDC
  - All admitted to hospital
  - Five required hemodialysis
- Fifteen of the patients were male; ranged in age from 15 to 33, no history of kidney disease
- In early Feb 2013, UA-Birmingham reported 4 cases of previously healthy young men, whose acute kidney injury was associated with synthetic marijuana
  - Symptoms of nausea, vomiting, and abdominal pain
  - All four men recovered kidney function, and none required dialysis
Testing

• NONE detected in standard urine tests
• GC/MS can detect up to 17 common ones
• LC-MS/MS can pick up several more
• Commercial blood tests can detect several
• Window: 48-72 hours
• Check with your local labs!
Management

• No antidote
• Contact 9-1-1 and transfer to ER
• Supportive care
• Benzodiazepines for agitation/anxiety
• In development: CB-1 antagonist [SR141716]-may reverse the effects
• Naltrexone may also attenuate effects
The Effect of Federal Controls on Synthetic Cannabis Calls to Poison Centers

- **March 2011**: DEA places JWH-018, JWH-073, JWH-200, CP-47, 497, and CP-497 C8 homologues into temporary Schedule I.
- **July 2012**: Synthetic Drug Abuse Prevention Act places more than a dozen synthetic cannabinoid homologues permanently into Schedule I.
- **April 2013**: Notice of Intent published to temporarily schedule UR-144, XLR 11, and AKB48.
Recent News

• Surge in synthetic cannabinoid exposures and poison control calls in April and May 2015
• Northeastern states and Southern states particularly effected
• NY: over 160 hospitalized following synthetic cannabinoid use in 2 weeks in April, 2015
Recent news: Poison control center calls

• 2013: 2668
• 2014: 3680
• 2015 through June 1: 3641
• New compounds: AB-Chimnaca, Fubinaca
• New street names: Blonde, Summit, Standard, Blaze, Red Dawn x, Citron, Green giant, Smacked, Wicked X, AK-47, Geeked Up, Ninja, Caution, Red Giant, Keisha Cole
Synthetic Cannabinoid Calls to U.S. Poison Centers (1/1/15-5/31/15)

PLEASE NOTE:
- These data are only representative of calls received by the poison centers and may not reflect the actual severity of the problem in the U.S. or any specific geographic location.
- As there is no mandatory reporting, there may be emergency room presentations and hospital admissions of which poison centers are unaware.
- Subject to the above bullets, these numbers are largely reflective of those users/abusers who have experienced adverse effects from the use of these products significant enough to warrant poison center or other health professional intervention; not all individuals who use/abuse such products call poison centers or visit emergency rooms.
- Nevertheless, the data are a good surrogate marker for rising use/abuse patterns and patterns of adverse medical outcomes associated with their use.
- For more information about the American Association of Poison Control Centers (AAPCC) data, please visit: http://www.aapcc.org/data-system/
Demystifying

HALLUCINOGENS
Nomenclature

• Hallucinogen
• Psychedelic [makes manifest the hidden realities of the mind]
• Psychotomimetic
• Entheogen [Generates the God within]
Hollister’s Criteria

• Changes in thought, perception, and mood predominate
• Intellectual and memory impairments minimal
• Stupor, narcosis, or excessive stimulation NOT integral effects
• Minimal autonomic nervous system side effects
• Addictive craving absent
Classic hallucinogens

• Hollister’s criteria PLUS
  1. Bind at 5-HT2 serotonin receptors
  2. are recognized by animals trained to discriminate 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from vehicle.
Prevalence
Prevalence

• Lifetime: 14.8%
• Past year: 1.8%
• Age 12-17: 4.1% lifetime/3.0% past year
• Males: 18.5%/2.3%
• Females: 11.3%/1.3%
• Caucasian: 17.8/1.9
• Black/African American: 6.6%/1.4%
• AI/AN: 28.3%/6.6%
• Asian: 5.5%/0.8%
• Hispanic/Latino: 9.5%/1.7%
Effects of hallucinogens- Somatic

- Dizziness
- Weakness
- Tremors
- Parasthesias
- Drowsiness
- Nausea
- Blurred vision
Effects of hallucinogens - perceptual

- Altered shapes and colors
- Difficulty focusing on objects
- Heightened sense of hearing
- Synesthesia - tasting colors, seeing music etc.
- Illusions
- True hallucinations - less common
- Altered sense of time
Other notable effects of hallucinogens

- Affective component - alterations in mood
- Anxiety/tension
- Depersonalization
- Dream-like state
- Difficulty expressing thoughts
Four stages of hallucinogenic experience

- Perceptual
- Biographical
- Symbolic
- Spiritual
“Bad trips”

- Challenging experiences
- Affective, perceptual
- Highly dependent on “set” and “setting”
- Use grounding techniques [deep breathing]
- Usually amenable to “talking down”
- May use benzodiazepines or antipsychotics for more difficult experiences
Classification

• Two subtypes of arylalkylamines
  1. Indolealkylamines- Bind to 5-HT2A, 2B, 2C, 1A
  2. Phenylalkylamines- selective for 5-HT2A

Note: Arylalkylamines can also be stimulants or empathogens based on their molecular structures
Indolealkylamines: substituted tryptamines

- DMT [N,N- Dimethyltryptamine]
- Ayahuasca
- Psilocybin/Psilocin
- Lysergamides [LSD]
- Beta-carbolines [harmaline]
Indolealylamines-lysergamides
Indolealylamines-lysergamides
Indolealylamines-lysergamides

turn on
tune in
drop out
PHENYLALKYLAMINES
Phenylalkylamines

• Largest group of classic hallucinogens
• Mescaline [peyote, San Pedro]
• 2-CB [“nexus”]
• DOM, DOB, DMA, MDA, many others
Peyote

- Sacramental use within Native American Church
- Grows within a 50 mile distance of Rio Grande along US-Mexico border, and in hills north of Mexico City
- Buttons harvested from top of peyote cactus
- Onset 30-60 min: nausea, increased respiration rate, minor perceptual changes
- Next several hours [5-10]: classic hallucinogen effects
DOM

• Very potent
• Results from structural modification of mescaline-like substances
• Used as model hallucinogen in drug discrimination studies
MDA

• Stimulant + hallucinogenic effects
• Modified to form MDMA [“ecstasy”]- stimulant + empathogenic effects
Endless combinations are possible

- By changing the molecular structure, you can get hallucinogen, empathogen, stimulant, or a combination of these three!
Alexander “Sasha” Shulgin

- Discovered, synthesized, and personally tested over 200 psychoactive substances for their psychedelic properties
- Authored PIHKAL, TIHKAL [Phenethylamines and Tryptamines I Have Known and Loved]
- Popular creations include the DOx creations [DOB, DOM], and 2C series [2CB, 2CI]
“Magical half dozen”

• DOM
• 2-CB
• 2-CE
• 2C-T-2
• 2C-T-7
• [mescaline]
2C-phenylethylamines

- A broad range of compounds that share a common phenylethan-2-amine structure.
- 2 C-X can be snorted or dissolved into a liquid and placed on blotter paper under the tongue.
- May last 6-10 hours; onset takes 15 min- 2 hours
2C-phenylethylamines

- Almost all of the 2C-phenethylamines are produced in Asia, principally China, but some small labs in the U.S. are capable of producing 2C (usually 2C-B).
- In 2011, DEA offices throughout the country began noting the increasing availability and abuse of 2C at raves and in nightclubs, particularly by teenagers and young adults.
2C-B [“Nexus”]

• Used by underground therapists in 1970s
• Create a warm atmosphere, ego weakening, therapeutic rapport
• ‘My body was flooded with orgasms - practically from just breathing. The love-making was phenomenal, passionate, ecstatic, lyric, animal, loving, tender, sublime....I am aware of every muscle and nerve in my body, unbelievably erotic, quiet and exquisite, almost unbearable..'
• Sold over the counter as a sexual enhancer worldwide until 1993
• Popular at raves; banned by DEA
2C-B [“Nexus”]

- ‘When I take Nexus, I merge with the music, become one with the crowd, and fuse with the whole of Planet Earth. This isn't a drug, it's a trance-dance sacrament.’
- ‘a cross between the warm, lovey-dovey feeling produced by Ecstasy and the visual patterning you get when you take magic mushrooms’
- ‘I tried it once and all that happened was that I felt jittery, disorientated and strung out for the entire evening.'
2C-I

• Became popular between 2001-2005
• Strong stimulant component, with associated hallucinogen and empathogen components
• Often delayed effect [users taking multiple doses as a result]
• Users report virtually no nausea, vomiting or muscle cramps [as opposed to 2C-T-2 and 2C-T-7]
• ‘deeper, more purely psychedelic and less sensory’ compared to 2C-B
2C-C-NBOMe, 2C-I-NBOMe, 25-I-NBOMe, Mescaline-NBOMe

- New class of 2C drugs
- NO history of human consumption prior to 2010
- Linked to several hospitalizations and deaths
- Usually result of people taking upto 10x the recommended doses
- “N-Bomb”, “Smiles”
2C-C-NBOMe, 2C-I-NBOMe, 25-I-NBOMe, Mescaline-NBOMe

- Strongly active at the sub-milligram dose (a Super Potent drug)
- Most 25I and 25C is sold as pure powder
  - Weighing and handling pure high-potency chemicals such as LSD or 25I-NBOMe should be performed wearing eye protection, gloves, and a filter mask
- Perhaps the greatest risk of the wide availability of pure NBOMe powders is confusing one white powder for another, or simply misunderstanding the difference between one psychedelic or stimulant drug and another
- In 2011, 10 items of the NBOMe family were seized and identified in NFLIS forensic laboratories, as compared to 447 in 2012.
**2C-C-NBOMe, 2C-I-NBOMe, 25-I-NBOMe, Mescaline-NBOMe**

- Effective November 15, 2013, the United States Drug Enforcement Administration (DEA) made the synthetic phenethylamines 25I-NBOMe, 25C-NBOMe, and 25B-NBOMe Schedule I, illegal drugs under the Controlled Substances Act (CSA) for the next two years.
- Plan to make them permanently illegal
Hallucinogen Persisting Perception Disorder (HPPD)

- Re-experiencing of perceptual symptoms experienced while intoxicated following cessation of use = flashbacks
- Unrelated to dose or number of exposures
- Usually resolves within 1-2 years of last use
- Can be triggered by other substance use
Conclusions

• Synthetic substances of abuse are evolving at a very rapid rate
• This has made it difficult for clinicians and law enforcement agencies to keep up
• It is imperative for us to understand these substances in order to better serve our communities