Synthetic Cannabis: Toxicological Considerations

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Origin of Synthetic Cannabis

• Synthetic marijuana refers to the many herbal mixtures inaccurately marketed as “safe” and legal, that produce marijuana-like effects. It is often labeled “not for human consumption” and sold as “incense,” but look more like potpourri. It may contain dried, shredded plant material and chemicals that create the mind-altering effects. People buy it in head shops, convenience stores, and on the Internet.
Origin of Synthetic Cannabis

• Huffman began his research on a class of chemicals found in marijuana, cannabinoids, in 1984. Over the course of 20 years – supported by generous grants from the National Institute on Drug Abuse (NIDA) – Huffman and his team developed more than 450 different synthetic cannabinoids that could mimic the effects of natural marijuana.

• Dr. Richard Huffman created the mixture at Clemson University and retired years ago, but some companies copied his synthetic marijuana compound and sprayed it onto potpourri leaves, creating the synthetic marijuana that is now leading to drug abuse problems all over the country.
Origin of Synthetic Cannabis

- Herbs are often sprayed with dried synthetic cannabis
- Synthetic Cannabis substitutes are not produced in a controlled environment
- Purity and dosage are not regulated or consistent
- The chemicals in synthetic marijuana are stronger and bind more permanently to the receptors in the body. The remain longer in the brain and organs
- They do not bind as quickly to receptors in the brain and this causes an increase risk of overdose due to not feeling the effects as quickly
- Use of synthetic cannabinoids is alarmingly high, especially among young people. Approximately 1 in 9 12th graders in America reported using synthetic cannabinoids in the past year. Synthetic cannabinoids are the second most frequently used illegal drug among high school seniors after “natural marijuana”
Synthetic Cannabis:

a) Naphthoylindoles

\[
\begin{align*}
&\text{JWH-018} & \text{JWH-073} \\
&\text{Sts-135} & \text{Pb-22} \\
&\text{JWH-081} & \text{UR-144} \\
&\text{JWH-122} & \text{A-796,260} \\
&\text{Urb-602} & \text{JWH-007} \\
&\text{AM-2201} & \text{MAM-2201} \\
&\text{AKB48} & \text{AM-1220} \\
&\text{XLR-11} & \text{5-Fluoropentyl-JWH-122}
\end{align*}
\]

b) Cyclohexylphenoles

\[
\begin{align*}
&\text{CP-47,497-C8}
\end{align*}
\]

SOURCE: Agudelo et al. (2012). Effects of Synthetic Cannabinoids on the Blood Brain Barrier, Presented at 74th Annual CPDD.
Origin of Synthetic Cannabis

- Synthetic marijuana began being sold in 2004
- It was marketed as a “legal high”
  - In 2011 five different types of synthetic marijuana compounds were added as Schedule I controlled substances.
- 2013: 400 different synthetic marijuana compounds identified, differing widely in chemical structure, potency, and receptor activation
Synthetic Cannabis Use
Synthetic Cannabis: AAPCC

• There were 2, 874 calls received by U.S. Poison Control Centers about synthetic marijuana in 2010.

• The limited research available indicates that synthetic marijuana may have the potential for dependence.

• It is estimated that 11, 406 U.S. emergency department visits in 2010 involved synthetic marijuana and three-fourths of these visits were made by patients ages 12-29.

• 59% of ED visits by patients involved synthetic marijuana and no other substances. 36% were a combination of 2 or more substances.

  Excerpts from Cesar Fax May 9, 2011
Synthetic marijuana

Red X Dawn

Yucatan Fire

Genie

Blaze
Synthetic Cannabinoids

- Wide variety of herbal mixtures
- Marketed as “safe” alternatives to marijuana
- Labeled “not for human consumption”
- Contain dried, shredded plant material (inert) and chemical additives that are responsible for their psychoactive effects.

Synthetic Marijuana

• Sold as “herbal incense”
  • Low odor

• Sold as “plant food”

• “Not for human consumption”

• Sold in tobacco shops, internet
Testimonials....

• 3 individual “hits” from a small pipe
• “Organic” taste/no chemical odor or taste
• 5 minutes: “Feels like cannabis”
• 10 minutes: “Like an intense cannabis high”
• “More than 3 puffs might be too much”

Synthetic Cannabis: Clinical Effects

• Elevated mood
• Feeling of relaxation
• Altered perception
• Stronger than marijuana
• Psychotic: extreme anxiety, paranoia, and hallucinations
  • Few scientific studies on effects on the human brain
  • Differing chemical compositions: likely some varieties contain unknown substances with dramatically different effects than the user may expect.
Synthetic Cannabis: Clinical Effects

• HIGH heart rate (“120-150”)
• HIGH blood pressure (“200/100”)
• Convulsions
• Anxiety attacks
• Disorientation
• Hallucinations and paranoia
  • Monsters demons aliens
  • Suicidal thoughts and actions
Synthetic Cannabis: Clinical Effects

- Insomnia
- Somatic pain
- Nausea
- Seizures
- Agitation
- Vomiting
- Internal restlessness
- Tremors
- Palpitations
- Headaches
- Perceptual alterations

- Visual and auditory hallucinations
- Paranoia
- Aggression
- Depersonalization
- Dissociation
- Anxiety
- Depressed moods
- Hypertension
- Hyperventilation
Cannabis vs. Synthetic Cannabinoids: Effects Seen in Clinical Cases

- **Most symptoms are similar to cannabis intoxication:**
  - Tachycardia
  - Reddened eyes
  - Anxiousness
  - Mild sedation
  - Hallucinations
  - Acute psychosis
  - Memory deficits

- **Symptoms **not typically seen** after cannabis intoxication:**
  - Seizures
  - Hypokalemia
  - Hypertension
  - Nausea/vomiting
  - Agitation
  - Violent behavior
  - Coma

Synthetic Cannabis: Withdrawal

• Withdrawal effects similar to withdrawal from marijuana:
  - disturbed sleep & dreaming, anxiety, craving, nausea, muscle twitching, chills...

• significant tolerance
Synthetic Cannabinoids: Other Considerations

• Unlike cannabis, synthetic cannabinoids have no therapeutic effects
  • Example: no cannabidiol (anti-anxiety), so mood effects unpredictable

• Packets can contain other psychoactive substances: opioids, oleamide, harmine/harmaline (MAO-Is) that can interact with the synthetic cannabinoid

• Cancer-causing potential of inhaling smoke from these compounds unknown
Synthetic Cannabis: Toxicology

- Mimics the effects of marijuana
- Act on the same receptors as marijuana
- Effects up to 800 times stronger than traditional marijuana.
Synthetic Cannabis: Toxicology

Symptoms of Synthetic Marijuana Use

OVERALL SYMPTOMS

- Increased Agitation
- Paranoid Delusions
- Depression
- Hallucinations
- Exaggerated Thoughts of Suicide
- Feeling of Impending Doom
- Panic Attacks
- Heart Attacks

“Glazed” expression, red eyes

Psychosis

Inability to Speak

Body Temperature Fluctuation, Inability to Feel Pain, Seizures

Increased Blood Pressure and Heart Rate, Heart Attack

Temporary Paralysis, Cramping

Kidney Failure

Vomiting

Please Call 911 IMMEDIATELY if you suspect someone has used Synthetic Marijuana!

Many of these symptoms may be life threatening and may change suddenly.

Graphic by To The Maximus Foundation. Please use with attribution.
Cannabinoids

• Neurobiological Concerns:
  • Shown to induce dopamine release (although less directly than stimulants) → brain reward signal → potential for compulsive use/addiction
  • Shown to impact regions of the brain responsible for coordination, problem-solving, sense of time, motivation, etc. → impaired when high
  • Effects on regions underlying learning and memory → possible long-term effects
  • Possible link to psychosis and schizophrenia
“Classic” Cannabinoids

• Endocannabinoid system ("endo" = within)
  Only recently discovered, unusual, not well understood
  • Receptors: CB1 (brain), CB2 (immune system)
  • Transmitters: Anandamide, 2-AG
• THC: binds to CB1 receptor
  • But not very well (low affinity) and not very good at inducing effects (partial agonist)
  • But unlike endocannabinoid transmitters, not degraded immediately, so CB1 activation is extended/exaggerated compared to anandamide
Synthetic Cannabinoids

- Little structural similarity to THC, but similar effects profile
  - Bind to CB1 and CB2 receptors
  - Same types of physical effects & impairments
  - In animals: signs of “high” similar, but at 2-14x lower dose
- The problem: Stronger & longer-lasting than THC
  - Better binding to receptors (high affinity/potency) AND each binding event has greater effect (full agonist)
    - 4x higher affinity for CB1, 10x for CB2
    - Longer half-life so effects longer lasting
  - Products of break-down (metabolites) also psychoactive
  - Together: More, more-likely, and longer-lasting adverse effects (especially if dosing is based on cannabis)
Synthetic Cannabinoids: “The Next Generation”

- New compound, URB-754: Does NOT bind to CB receptors itself, but inhibits enzyme that breaks down endocannabinoids
  - More endocannabinoid around $\rightarrow$ more binding to receptors
- AND, one “spice” sample was found to contain URB + a cathinone, which reacted with one another and together created a whole new psychoactive compound
Synthetic Cannabis: Urine Drug Screening

• Poorly detected on routine urine drug screens

• Cost for GC/MS is approximately $75 to $100 per group

• Detection correlates poorly with toxicity

• Creates numerous problems for law enforcement
Synthetic Cannabis: Clinical Consequences

- 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
Synthetic Cannabis: Clinical Consequences

• Leads to symptoms similar to those caused by dangerous conditions known as preeclampsia and eclampsia
  • Preeclampsia is marked by high blood pressure and a high level of protein in the urine
  • Preeclampsia can lead to eclampsia, which can cause a pregnant woman to develop seizures or coma, and in rare cases is fatal
A woman (35 weeks pregnant) suffered a seizure and appeared agitated
  - High blood pressure and protein in urine, treated for eclampsia
  - An emergency C-section was performed (baby in distress)

The woman screened negative for drugs, but an anonymous caller reported the woman regularly smoked “Spice Gold,” a synthetic cannabinoid.
  - Spice Gold cannot be detected with a standard urine test.

The baby tested negative for drugs.

The woman required psychiatric care for psychotic behavior the day after delivery.
  - “This was not a pregnancy problem but a drug problem. Eclampsia is cured with delivery of the baby, but she did not get better after delivery.” (Dr. Cindy Lee)
Lethal outcomes

• Synthetic cannabinoid use has been associated with lethal outcomes.

• Pre-existing conditions may produce greater risk for a fatal case outcome.

• Differences of opinion exist regarding cause and manner of death determination.
Lethal outcomes

• Adverse effects associated with synthetic cannabinoid use include agitation, psychosis, seizures and cardiovascular effects, all which may result in a lethal outcome.

• 2016 Case series: 25 medical examiner and coroner cases where the presence of synthetic cannabinoids was analytically determined.

• Synthetic cannabinoid drug use as a cause or contributory cause of death

• Insufficient information exists to correlate blood synthetic cannabinoid concentrations to effect, in the absence of other reasonable causes
Synthetic Cannabis: What Now?

• A Year After Federal Legislation Bans Synthetic Drugs, More Than 250 Types Still Sold

• Legislators and law enforcement agencies are trying to keep up with drug makers, who are continually introducing slight variations of their products to keep one step ahead of the law.

• From January to August 2013, poison control centers received 1,821 calls regarding exposures to synthetic marijuana.
  • synthetic drugs are unregulated, users don’t know what they are actually getting when they buy the products in gas stations or online.
Synthetic Cannabis: What Now?

• The trend for synthetics will continue to evolve and adapt to current fads, laws and drug screens. There is now a cemented culture of synthetic drugs and it will continue to maintain itself.

• Providers, schools, communities and families need to educate themselves about these new substances but keep in mind that it all comes back to substance abuse/addiction and the desire to experiment and get high. That is not a new concept and there are treatment programs available.
Summary

• Lack of information on the chemical contents, dosage levels, and consistent quality of the products is a major problem since users are taking drugs about which they know little, which makes provision of health care for adverse events more difficult.

• Despite widespread Internet availability and use among certain populations, health care providers remain largely unfamiliar with synthetic drugs and the multiple variations which have appeared recently.
Summary

• Research is needed to better understand the side effects and long-term consequences associated with the use of synthetic cannabinoids and synthetic cathinones.

• More toxicological identification of these new drugs, more information on the sources of them, as well as their distribution and patterns of use is needed to curtail future increases in use.
Summary

- We do not have human neurobiological data or long-term data, but we can extrapolate a few key points from the existing literature:
  - Synthetics vs. Classics: Neurobiological concerns hold up, plus more
  - In all cases, neurobiology predicts abuse potential
  - In general, synthetic versions are not a simple substitute for “classics” – effects tend to be more intense (including side effects), some unexpected, and some new interactions that were not a concern before