Spice, K2 and Other Emerging Synthetic Drugs

13th Annual Summer Institute
July 19, 2011

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TASC, Inc.
Emerging Drug Trends

- Synthetic Cannabinoids
  - Spice / K₂

- Stimulants
  - “Bath Salts”
  - Plant Extracts
Spice & K₂: Synthetic Cannabinoids
Synthetic Cannabinoids

- Most common products:
  - Spice and K2
- Sold in head shops and online
- Many varieties/scents
- Labeled and sold as incense: “Not for Human Consumption”
Bay Bean, Blue Egyptian Water Lily, Dwarf Skullcap, Indian Warrior, Lions Tail, Indian Lotus, Honeyweed or Motherwort, Marshmallow, Rosehip...
Most of the herbal components have very little to mild psychoactive effects, although some traditional herbalists may disagree. At most, they may:

- Add color and flavor
- May have mild relaxing properties
- Decrease blood pressure
- Reduce inflammation
- Induce mild euphoria
Varieties of Herbal Incense

- Various Products Available
  - Spice, K2, Smoke, Yucatan Fire, Hush, Genie
Single Use or Bulk Product

Sold Loose or in joint form
Many of these herbal products have been sold for years as legal alternatives to marijuana.

Unlike many “legal weed” products sold in the past, these new products are giving measured physiological effects, often in the uninitiated or novice drug user.

So where is the high coming from?
Intense psychoactive properties were being reported, but with little verification.

In late 2008, forensic analyses conducted in Europe identified JWH-018 as a psychoactive ingredient in many of these products.

Investigation revealed that Synthetic Cannabinoid compounds are being sprayed on herbal product to produce THC-like physiological effects.

Product is surreptitiously laced with potentially harmful chemicals under the guise of herbal incense not for human consumption.
Spice vs. Marijuana

- More expensive than marijuana (~2x)
- No standard Spice\K2 blend on market
- Significant hangovers when used with alcohol
- Much harsher effect on throat and lungs
- Intense high but shorter ~30 minutes
Cannabis Overview

Used for more than 4000 years for euphoric and therapeutic effects

Most commonly abused drug in the world.

Roughly 4% of the world's adult population (162 million people) use cannabis annually, and about 0.6% (22.5 million) use it on a daily basis.
Cannabis

Contains:

>450 chemicals
>60-90 different cannabinoids

$\Delta^9$-Tetrathydrocannabinol (THC)
Main psychoactive ingredient of marijuana
THC content in marijuana varies – typically 2-5% in cannabis, but much higher has been found.

Marijuana users may experience stimulant, depressant, and/or hallucinogenic properties.

Most commonly used for hallucinogenic effects.

Most individuals self-titrate their THC intake.
Most common Medicinal Uses:

- Relief from nausea and vomiting
- Stimulation of appetite
- General analgesic effects (pain reliever)
- Lowered intraocular eye pressure
What are Cannabinoids?

Class of chemicals that may have similar structure and/or activity that mimic:

- **Phytocannabinoids** (found in cannabis plants)
  - Natural, herbal, classical

- **Endocannabinoids**
  - (found in CNS and immune systems of animals)
What are the Endocannabinoid functions?

Signaling molecules (Lipid messengers) that are released from cells to bind to nearby cell receptors.

Signaling is retrograde (reverse direction postsynaptic to presynaptic neurons)
At least two subtypes of Cannabinoid Receptors:

**CB₁ Receptor**

Found throughout the peripheral and CNS systems

**CB₂ Receptor**

Found throughout the peripheral nervous system and associated with the immune system
cannabinoid CB1 receptor

synaptic cleft

endogenous ligands: anandamide, 2-arachidonoylglycerol, palmitoylethanolamide

post-synaptic membrane

cytoplasm

inhibitory G-protein

Illustration from CNSForum.com
Illustration from CNSForum.com

nerve terminal

Na⁺ channel

MAP kinase

krox 24

N and P/Q type voltage dependent Ca²⁺ channel

CB₁

protein kinase

phosphorylation

A-type K⁺ channel

inwardly rectifying K⁺ channel

tetrahydrocannabinol (Δ⁹-THC)-the active ingredient of cannabis

cannabinoid CBI receptor

ATP

adenylate cyclase

cAMP

synaptic cleft
THC Tolerance

- Downregulation – receptors from cell surface are removed by internalization; synthesis
- Desensitization of CB1 receptors as Δ9-THC tolerance develops – the uncoupling of G proteins
Four Groups of Synthetic Cannabinoids:

- THC Analogue (classical)
- Non-classical – Cyclohexylphenyl (CP) series
- Aminoalkylindoles – (JWH compounds)
- Other – Fatty Acid Amides
Many are full CB₁ & CB₂ receptor agonists

Originally investigated for medicinal purposes:

- Analgesics
- Weight management
- Control of Nausea
- Smoking cessation
Cannabinoid Agonists

- THC Analogues
  - HU-210, HU-211, HU-243,
  - HU-308, HU-320, HU-331,
  - HU-336, HU-345

Raphael Mechoulam
Hebrew University
Cannabinoid Agonists

Cyclohexylphenyl (CP) Series

Pfizer Pharmaceutical

CP 47,497, CP 55,940,
CP 47,497 – (C8),
CP 50,556-1, CP 55,244
Cannabinoid Agonists

Aminoalylindoles

Over 470 analogues
JWH-015, JWH-018, JWH-019,
JWH-073, JWH-081, JWH-122,
JWH-133, JWH-147, JWH-171,
JWH-210, JWH-250, JWH-398

John W. Huffman

Clemson University
## Synthetic Cannabinoid Agonists

<table>
<thead>
<tr>
<th>Product</th>
<th>JWH-018</th>
<th>JWH-073</th>
<th>CP 47,497</th>
<th>JWH-250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spice Gold</td>
<td>20 mg/g</td>
<td>11 mg/g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spice Diamond</td>
<td>17</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spice Maxx</td>
<td>17</td>
<td>0.07</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Spice Silver</td>
<td>9</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Space</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2 Blonde</td>
<td>12</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2 Standard</td>
<td>9</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2 Citron</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2 Summit</td>
<td>11</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2 Blue</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2 Pink</td>
<td>11</td>
<td></td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>K2 Latte</td>
<td>16</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2 Mint</td>
<td>19</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2 Silver</td>
<td>8</td>
<td></td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Herbal Blends</td>
<td>2-36</td>
<td></td>
<td>1-17</td>
<td></td>
</tr>
</tbody>
</table>

Table Data Compiled by NMS Labs
Experiences

- Milder high
- More intense side effects
  - Rapid heart rate
  - Body aches
  - Paranoia
Experiences

Autwarter et. al.: University Medical Center in Freiburg Germany

Authors self-dosed with 0.3g Spice Diamond cigarette

- Reddened Conjunctiva
- Increased pulse rate
- Xerostomia
- Mood alteration and perception
- No psychomotor abnormalities, but felt impaired
- Hangover throughout following day

Toxicology identified JWH-018 and CP-47,497

- Michelle Glinn, PhD, Michigan State Police
Adverse Effects

Physiological

- Raised blood pressure and heart rate
- Bloodshot eyes
- Swaying
- Slurred speech
Adverse Effects

Psychological

- Anxiety, Agitation
- Paranoia and Hallucinations
- Seizures and convulsions
- Short-term memory loss
- Time dilation
### DRE Evaluation

Regular user of THC and K2. Dosed with K2 containing JHW-018 and JWH-073

<table>
<thead>
<tr>
<th>Metric</th>
<th>Pre-Dose</th>
<th>Post-Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-Leg Stand</td>
<td>No Errors</td>
<td>Swayed, bent knees, leaned, nearly fell</td>
</tr>
<tr>
<td>Walk-and-Turn</td>
<td>One error during turn</td>
<td>Incorrect turn, more deliberate steps</td>
</tr>
<tr>
<td>Romberg</td>
<td>No sway</td>
<td>Visible sway</td>
</tr>
<tr>
<td>Finger to Nose</td>
<td>Problems locating tip of nose</td>
<td>Did better than pre-dose</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>None present</td>
<td>None present</td>
</tr>
<tr>
<td>Convergence</td>
<td>Normal</td>
<td>Left eye unable to converge</td>
</tr>
<tr>
<td>Pupils</td>
<td>6.5 mm</td>
<td>6.5 mm; slowed reaction to light; rebound dilation</td>
</tr>
<tr>
<td>Eyes</td>
<td>Normal</td>
<td>Bloodshot, droopy</td>
</tr>
<tr>
<td>Eyelids</td>
<td>Normal</td>
<td>Tremors</td>
</tr>
<tr>
<td>Muscle</td>
<td>Normal</td>
<td>Tremors; tone normal</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>98</td>
<td>114</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>150/104</td>
<td>148/102</td>
</tr>
<tr>
<td>Temperature</td>
<td>98.8</td>
<td>99.5; skin warm to touch</td>
</tr>
</tbody>
</table>

- Michelle Glinn, PhD, Michigan State Police
Statistically significant, dose-dependent, region-specific decreases in cannabinoid binding observed in all brain regions examined following 4 and 14 days of treatment.

The pattern of CB1 receptor down-regulation was similar to that observed in adults treated with cannabinoids; however, the magnitude of down-regulation was smaller in adolescents.

This reduced compensatory response in juveniles may contribute to some acute behavioral effects, the pharmacological cross-tolerance and the long-lasting, adverse psychological consequences of cannabinoid exposure during adolescence.
20-year old patient reported that he had smoked "Spice Gold" daily for 8 months.

He developed tolerance and rapidly increased the dose to 3g per day. He felt a continuous desire for the drug and kept on using it despite the development of persistent cognitive impairment.

Urinary drug screens were negative on admission to the hospital, as they were again on discharge.

On hospital days 4–7, he developed inner unrest, drug craving, nocturnal nightmares, profuse sweating, nausea, tremor, and headache.

His blood pressure was elevated for two days, with a maximal value of 180/90 mm Hg accompanied by a heart rate of 125/min.

The patient stated that he had experienced a similar syndrome a few weeks earlier during a phase of abstinence owing to a short supply, and that it had quickly subsided after he had started consuming "Spice" once again.
Federally Banned Cannabinoids (March 2011)

Δ9-THC

JWH-018

JWH-073

CP-47,497

Cannabicyclohexanol

JWH-200
Additional AZ Banned Cannabinoids (Feb 2011)

Δ9-THC

JWH-015

JWH-019

HU-210

JWH-250

JWH-398
Detection

- No standards set for Spice/K2 detection
  - Legal cutoff not set
  - Relatively new in Forensic Drug Testing industry

- Metabolism not well-defined
  - Purified standards continue to be synthesized

- Sample Media Variability
  - Urine – Only metabolites observed
  - Oral Fluid – Parent drug found

- Testing methodologies still in development
  - Many methods for isolating compounds from sample matrix
  - Varying sensitivity of instrumentation
Most compounds are **not** detected by standard drug screening tests (Negative on THC screen)

Detection period roughly 24-72 hours in urine
- Based on *current* knowledge and observations
- Only metabolites are detected in urine
- Typically JWH metabolites analyzed due to availability of standards

Approximately 8-48 hours in blood and oral fluid
- Parent drug detected

Advanced testing methodology utilized
- Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS)
- Expensive
Analysis by LC/MS/MS
# AZ Juvenile Probation Stats

<table>
<thead>
<tr>
<th>Population</th>
<th>Total Samples</th>
<th>Positive Spice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maricopa Probation</td>
<td>449</td>
<td>39.6%</td>
</tr>
<tr>
<td>Maricopa Transferred Youth</td>
<td>59</td>
<td>54.2%</td>
</tr>
<tr>
<td>Yavapai Probation</td>
<td>46</td>
<td>41.3%</td>
</tr>
<tr>
<td>Pima Probation</td>
<td>8</td>
<td>25.0%</td>
</tr>
<tr>
<td>Mohave Probation</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>Pima Drug Court</td>
<td>36</td>
<td>30.6%</td>
</tr>
<tr>
<td>Maricopa Drug Court</td>
<td>69</td>
<td>37.7%</td>
</tr>
<tr>
<td>Yavapai Drug Court</td>
<td>17</td>
<td>41.2%</td>
</tr>
<tr>
<td>Mohave Drug Court</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>687</strong></td>
<td><strong>40.2%</strong></td>
</tr>
</tbody>
</table>

From Arizona TASC: Feb to Mid-Jul 2011
## AZ Adult CJ Population

<table>
<thead>
<tr>
<th>Population</th>
<th>Total Samples</th>
<th>Positive Spice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maricopa Drug Court</td>
<td>475</td>
<td>22.1%</td>
</tr>
<tr>
<td>Yavapai Probation</td>
<td>120</td>
<td>15.8%</td>
</tr>
<tr>
<td>AZ Adult Parole</td>
<td>23</td>
<td>30.4%</td>
</tr>
<tr>
<td>Coconino Probation</td>
<td>13</td>
<td>69.2%</td>
</tr>
<tr>
<td>Pima Probation</td>
<td>8</td>
<td>75.0%</td>
</tr>
<tr>
<td>Mohave Probation</td>
<td>9</td>
<td>22.2%</td>
</tr>
<tr>
<td>Yuma Probation</td>
<td>3</td>
<td>66.7%</td>
</tr>
<tr>
<td>LaPaz Probation</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>652</strong></td>
<td><strong>23.0%</strong></td>
</tr>
</tbody>
</table>

From Arizona TASC: Feb to Mid-Jul 2011
No standards set for Spice/K2 detection
  - Legal cutoff not established
  - Relatively new in Forensic Drug Testing industry

Metabolism not well-defined
  - Purified standards continue to be synthesized

Sample Media Variability
  - Urine: Only metabolites observed – not well-defined
  - Oral Fluid: Parent drug found – possible shorter detection period

Testing methodologies still in development
  - Many methods for isolating compounds from sample matrix
  - Varying sensitivity of instrumentation
Future Challenges

- Hundreds of potential compounds can be used in the manufacturing process of Spice products
- Limited number of banned chemicals on the books
- Moving target – Spice industry responds to legislation, Laboratories must respond in kind
- Lack of complete understanding of metabolism
- Lack of certified metabolite standards (getting better)
Synthetic Cannabinoids of Interest?

Δ9-THC

HU-210*

WIN 55,212

JWH-133

* Banned in AZ
Drug Development: Rimonabant

(SR141716) Antiobesity drug

Antagonist of CB1 receptor - Possible use to mediate CB1 cannabinoid pharmacodynamics by blockade of agonists

- Decrease in heart rate (BPM)
- Reduced cannabis effects of 40-75% in single dose or multiple small dosing
- No significant cannabis withdrawl
- No clinical adverse effects
Rimonabant (cont’d)

First CB1 Receptor antagonist on the market, used in conjunction with diet and exercise for weight loss.

Other Uses:
• Assisted in smoking cessation therapy
• Addiction reduced cocaine-seeking responses by 2 of 3 most common triggers in relapse (priming and cues)
• Possible reduction of ethanol and opiate-seeking behavior
• Hypothetically could improve short-term memory (in rats)
• Blocks psychoactive and cardiovascular effects of THC without affecting the pharmacokinetics

FDA supported its use for obesity in 2006 but never was brought to market after failure to demonstrate safety by the manufacturer. Benefits deemed no longer outweighing the risks – pulled in 2009
Bath Salts and Other Stimulants
Bath Salts

Sold in head shops, gas stations and online

Psychoactive / Dissociative

Illegal in many states

Highly addictive and dangerous

Snorted, but can be smoked, taken orally or injected
4MMC, Meow-meow, MC, MTV, M-CAT, Bounce, Plant Food
$30-90 / gram - talc-like

Usually imported from
China / Asia

Pixie Dust, Ivory Wave, Ocean, Charge Plus, White Lightning, White Girl, Scarface, Hurricane Charlie, Vanilla Sky, Bonzai, Grow, Blue Silk, Lovey Dovey...
Chemical Composition

Mephedrone - 4-methylmethcathinone (4-MMC)

AKA: Meph, drone, MCAT

- Originally developed in 1929 - recently “rediscovered”
- Analogue to other controlled substances
- Sold as plant food or bath salts – not for human consumption
MDPV (3,4-methylenedioxyxypyrovalerone)

AKA: MDPK, Magic, Super Coke, MTV and PV

- Originally developed in the 60’s for chronic fatigue and appetite suppression.
- Abuse and dependence a problem with a compulsive desire to continuously re-dose
- Similar in structure to MDMA, but more of a stimulant
- Only has mild empathogenetic or entactogenic properties
Stimulant Effects

- Effects last 2 - 4 hours
- Amphetamine-like high similar to cocaine (not as intense)
- Feelings of euphoria - Increased alertness
- Dilated pupils
- Slurred speech in some, Inability to stop talking
- Increased heart rate
- Both decreased and/or increased sexual function/desire
Adverse Effects

Physical:
- CNS stimulant
- Increase BP and heart rate
- Chest pain, heart attack, stroke

Psychological:
- Delusions, paranoia, psychosis
- Personality disorders
- Depression when not using – as long as several weeks

After effects such as tachycardia, hypertension, and mild stimulation lasting from 6 - 8 hours
Lines of pure Mephedrone snorted by teen-ager thinking it was purified Ecstasy. Passed out – woke next day to:

- Shakes and tremors
- Hyperventilation
- Cold sweats

Hospitalized – symptoms lasted several days

Juvenile recovered
Abuse and dependence a problem with a compulsive desire to continuously re-dose

Some are constantly chase that first high

Mephedrone reduces to 4-methylephedrine - a known Cardiotoxic compound

Crushing chest pain – common redosing the cause?

Long-term effects of use are still being evaluated
Benzylpiperazine (BZP)

3-Trifluoromethylphenylpiperazine (TFMPP)

AKA: Legal X

- Originally developed for use as anti-parasitic agents for farm animals
- Potential as antidepressant in 1970s
- Alternatives to MDMA
- Evokes release of serotonin
Other Stimulants

Cathinone

- Found in the shrub *Catha edulis* (Khat)
- Part of the Middle East culture
- Stimulant typically extracted from chewing fresh leaves
Methcathinone

- First synthesized in 1928
- It was used in the Soviet Union during the 1930s and 1940s as an anti-depressant.
- Since the 1960s, methcathinone has been used as a recreational drug in the (former) Soviet Union.
Stimulant Structures

- Amphetamine
- Methamphetamine
- Cathinone
- Methcathinone
- Mephedrone
- MDMA
- MDPV
Most compounds are **not** detected by standard drug screening tests

Detection period roughly 24-72 hours in urine

Analyte-specific methodologies are used

- Gas Chromatography/Mass Spectrometry (GCMS)
- Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS)

Specialized Stimulants Panel:
- Amphetamine / Methamphetamine
- MDA / MDMA
- Cathinone / Methcathinone
- Mephedrone / MDPV
- BZP / TFMPP
Questions and Commentary
Contacts

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Thank You!