Spice, Bath Salts and Salvia, oh my!: A review of “on-trend” synthetic substances of abuse

Snehal Bhatt, MD Assistant Professor, Psychiatry
Medical Director, Addiction and Substance Abuse Programs
Objectives

• Identify the mechanism of action of some prevalent synthetic drugs of abuse.
• Recognize the psychological and physiological effects of these substances.
• State how emerging drugs of abuse are forever changing and involve manipulation of basic chemical structures to avoid legal ramifications.
• Describe some of the management strategies for these substances.
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

- LSD: 2.10%
- Hallucinogens: 5.0%
- MDMA: 3.8%
- Synthetic Cathinones: 1.3%
- Synthetic Cannabis: 11.3%
- Marijuana: 36%

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

- Alcohol: 57%
- Marijuana: 39%
- Synthetic Marijuana: 12%
- Rx Pain Relievers: 10%
- Rx Stimulants: 9%
- Ecstasy: 8%
- Cocaine: 7%
- Inhalants: 7%
- OTC Cough Medicine: 7%
- Crack: 4%
- Methamphetamine: 4%
- Salvia: 4%
- Bath Salts: 3%

"SPICE" [SYNTHETIC CANNABINOID]

What is it? Is it safe?
Anandamide- Endogenous cannabinoid
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 2
Comparisons between synthetic and natural cannabis effects (self-rated from 1 to 10).

<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 (2.36)</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% effectes 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 upto 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
Effects of legislation

- **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.
“BATH SALTS” [SYNTHETIC CATHINONES]
Media sensationalism

• Summer 2012 Florida: 31 y/o man Rudy Eugene chewed down the face of homeless man Ronald Poppo
• Prompted media reports of zombie cannibalism caused by bath salts
• Ultimately turned out: man had no traces of synthetic cannabinoids, cathinones or LSD in his system!
Other media reports

• The man who slashed himself to remove the “wires” in his body

• The mother who left her demon-ridden 2-year-old in the middle of the highway

• The 21-year-old son of a family physician who, after snorting bath salts once, shot himself following 3 days of acute paranoia and psychosis, including hallucinations of police squad cars and helicopters lined up outside his house to take him away
KHAT
KHAT

• Catha edulis: Shrub native to East Africa and Southern Arabia
• Leaves chewed socially for mild stimulant effect
• Quite prevalent in Somalia, Ethiopia, Yemen [over 10 million users]
• 1st described in 11th century
• Active substance: cathinone
• Euphoria, elation, increased alertness
• Tachycardia, hypertension
• Effects 90 minutes to 3 hours, but “sessions” lasting many hours
From khat to designer drugs!

- Cathinone > methcathinone [1928]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Alternative names</th>
<th>Product names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cathinone</td>
<td></td>
<td>Khat</td>
</tr>
<tr>
<td>Methcathinone</td>
<td>Ephedrine, β-keto-methamphetamine</td>
<td>Bubbles, Meow Meow, MCAT</td>
</tr>
<tr>
<td>Mephedrone</td>
<td>4MMC (4-methylmethcathinone)</td>
<td>Explosion, Impact</td>
</tr>
<tr>
<td>Methedrone</td>
<td>4-Methoxymethcathinone, β-keto-PMMA, PMMC</td>
<td>Energy-1, NRG-1</td>
</tr>
<tr>
<td>Methylone</td>
<td>B-keto-MDMA, MDMC</td>
<td></td>
</tr>
<tr>
<td>Naphyrone</td>
<td>Naphthlypyrovalerone</td>
<td></td>
</tr>
<tr>
<td>Butylone</td>
<td>β-keto-MBDB</td>
<td></td>
</tr>
<tr>
<td>4-Flouroemethcathine</td>
<td>4-FMC, flephedrone</td>
<td></td>
</tr>
<tr>
<td>3-Flouroemethcathine</td>
<td>3-FMC</td>
<td></td>
</tr>
</tbody>
</table>
History

• 1928: Methcathinone isolated
• 1988: Cathinone listed as Schedule I by UN Convention on Psychotropic Substances
• 1990s: outbreaks in Europe and US
• 1993: Schedule I substance by DEA
• 2007: Mephedrone appears in Australia and Europe
History

• 2009: Mephedrone appears in US
• 2010: MDPV and Methylone appear in US
• 2011 first 6 months: US poison controls 6x as many calls of “bath salt” exposure as 2010
• 2009-2010: 20 fold increase in drug seizures with synthetic cathinones
• September 2011: DEA issues a notice of intent to temporarily schedule three synthetic cathinones [mephedrone, methylone, and MDPV]
Marketing

- “legal highs”
- Cheap
- Sold in head shops and online
- “Not for human consumption”
Pharmacology

• Synthetic cathinones = B-ketophenethylamines
• Structurally similar to methamphetamine, but LESS potent

Fig. 2 Structural similarity of mephedrone (left) and methamphetamine (right)
Molecular structures

- Methamphetamine
- Methcathinone
- 4-Methylmethcathinone (Mephedrone)
- 3,4-Methylenedioxymethcathinone (Methylone)
- 3,4-Methylenedioxypyrovalerone (MDPV)
Pharmacology

- strongly inhibit reuptake of dopamine [like cocaine], serotonin [like MDMA], and norepinephrine [MDPV; 10x more potent than cocaine]
- Lime methamphetamine, increase pre-synaptic release of these substances [mephedrone]
- So, in a way, like a combination of cocaine and methamphetamine
- May also insert into DNA to exert toxicity
Pharmacology

• DA reuptake: MDPV >> cocaine, meth, methcathinone > mephedrone, methylone > cathinone > MDMA
• 5-HT reuptake: MDMA > cocaine, mephedrone >> meth, MDPV, methcathinone, cathinone
• NE reuptake: MDPV > meth, methcathinone > cathinone, mephedrone > MDMA, cocaine, methylone
Pharmacology

- DA release: meth, cathinone, methcathinone, mephedrone > MDMA
- 5-HT release: MDMA, methylone > mephedrone >>>>>> meth, methcathinone
Use

- White or brown powder; often in capsules
- Nasal, oral, rectal, IV/IM
- Onset of action: 30-45 minutes
- Duration of action: 3-7 hours
- MDPV stronger than mephedrone
Clinical Effects

- Euphoria, alertness, energy, talkativeness, sexual arousal
- Compulsion to re-dose!
- Sessions can last hours to days!
- Aggression/psychosis
- Phenomenal physical strength [like PCP]
- Bizarre behaviour
- Self mutilation
- Paranoia
- Suicide attempts
Clinical Effects

- Dependence/craving
- Sympathomimetic toxicity
- Hypertension
- Tachycardia
- Hyperthermia
- Dehydration
- Seizures
- Palpitations
- Headaches
- Chest pain
- Bruxism
- MI
- Myocarditis [mephedrone]
- Serious infections reported
- Death
Clinical Symptoms of Synthetic Cathinone Use in Patients Admitted to the Emergency Department (N=236)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>82%</td>
</tr>
<tr>
<td>Combative/Violent behavior</td>
<td>57%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>56%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>40%</td>
</tr>
<tr>
<td>Paranoia</td>
<td>36%</td>
</tr>
<tr>
<td>Confusion</td>
<td>34%</td>
</tr>
<tr>
<td>Myoclonus/Movement disorders</td>
<td>19%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>17%</td>
</tr>
<tr>
<td>CPK elevations</td>
<td>9%</td>
</tr>
</tbody>
</table>

Detection

- None detected on routine screening
- May cause false positive amphetamine screen
- GC-MS and LC-MS kits available commercially to detect mephedrone, MDPV and methylone
Clinical management

• Call 9-1-1; get to ER
• No antidote
• Supportive care; A-B-Cs
• Benzodiazepines for aggression/agitation
• Avoid B-blockers
• Sedation
• Passive or active cooling for extreme hyperthermia
• EKG/cardiac monitoring
• Serial temperature checks
• CPK, electrolytes, renal/liver functions, cardiac enzymes
Clinical Management

• Monitor until symptoms resolved
• 26% admitted to ICU
• 14% admitted to medical floor
• 9% admitted to psych floor
• 51% discharged from ER
Effects of legislation

Federal Efforts to Ban Synthetic Cathinones:

• Oct 2011: DEA exercised its emergency scheduling authority to control some of the synthetic substances used to manufacture bath salts; these synthetic stimulants are now designated as Schedule I substances.

• July 2012: Congress passed and President Obama signed the Synthetic Drug Abuse Prevention Act (MDPV and mephedrone Schedule I).

• April 3013: DEA places methylone into Schedule I.
SALVIA DIVINORUM
Info

• Mint family
• Use dates back centuries
• Religious rituals and herbal healing by Mazatec people- chew leaves or make a tea
• Last decade: a surge in use among teenagers/young adults- smoke
• 2008 DEA report: 1.8 million had tried
Also called

• Diviner’s sage
• Mystic sage
• Magic mint
• Sally D
• Maria Pastora
• Purple sticky
Pharmacology

- Salvinorin-A
- NOT a classical hallucinogen; no 5-HT2 binding
- Kappa opioid agonist- hallucinations, diuresis, spinal analgesia, sedation, depression, aversion
- NO respiratory suppression
- Hallucinations within seconds; duration of effect 20-30 minutes
Clinical effects

• “unique” intense high
• Meditation/trance state
• Hallucinations
• Distortions of perception
• Synesthesia
• Out of body experiences
• Depression in some; anti-depressant effect in some!
• Extreme dysphoria and anxiety; fractured reality
• Often ingested with alcohol and cannabis
Clinical Effects

• NOT reinforcing
• Very little addictive potential
• In fact, may have some role as a modulator of reward pathway
• May also have utility as a treatment for depression and anxiety, or as an anti-inflammatory
Testing/Management

- No good available methods for testing
- Few case reports of emergency care
- No antidote
- Benzodiazepines
- Supportive care
- Naltrexone
KRATOM
Info

- Legal plant product
- Used for centuries to treat opioid withdrawal
- Available on-line
- Derived from Mitragyna speciosa, a south asian tree
- Opioid-like effects: mild stimulant at low does, and analgesia at higher doses
- DEA” ‘drug of concern”
- One of top 5 legal highs in UK
Pharmacology

• Tree has 25 alkaloids
• Mitragynine is the opioid-like alkaloid
• Structurally distinct from opiates, yet acts as mu and delta agonist
• 13x more potent than morphine
• Onset: 5-10 minutes
• Duration: several hours
Uses

- Available as powder, leaves, or gum
- Smoked or brewed into tea
- Treatment for muscle pain
- Relief of opioid withdrawal
- Supposed benefits: anti-inflammatory, analgesia, anti pyretic, antitussive, antihypertensive, hypoglycemic, anti-malarial, anti-diarrheal
- Adverse effects: tolerance/withdrawal; seizures; hepatic damage
Detection/management

• No readily available detection kits
• Management: airway management
• Naloxone
• Benzos for seizures
• Treatment for opioid dependence
PIPERAZINE DERIVATIVES
Info.

- Piperazine= antihelminthic agent
- Has amphetamine like effects
- BZP schedule I since 2004
- 2010: 26% of clubgoers in UK used these substances
- Also rising rates in US
- “Legal ecstasy”
- “Benzo Fury”
- “MDAI”
- “Head Rush”
- “XXX Strong As Hell”
- “Exotic Super Strong”
### Common piperazines

<table>
<thead>
<tr>
<th>Abbreviated name</th>
<th>Chemical name</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZP</td>
<td>1-Benzylpiperazine</td>
</tr>
<tr>
<td>CPP</td>
<td>1-(3-Chlorophenyl)piperazine</td>
</tr>
<tr>
<td>MBZP</td>
<td>1-Methyl-4-benzylpiperazine</td>
</tr>
<tr>
<td>MEBP</td>
<td>N-(3-methylbenzyl)piperazine</td>
</tr>
<tr>
<td>MeOPP</td>
<td>1-(2-Methoxy-phenyl)piperazine</td>
</tr>
<tr>
<td>MeP</td>
<td>1-Methyl-3-phenylpiperazine</td>
</tr>
<tr>
<td>TMFPP</td>
<td>1-(3-Trifluoromethylphenyl)piperazine</td>
</tr>
</tbody>
</table>
Pharmacology

• BZP: inhibits serotonin reuptake; also a serotonin receptor agonist
• TMFPP: Release of endogenous stores of serotonin [like MDMA]
• Sold as pills containing multiple chemicals
• 75-150 mg
• Onset >2 hours after dose, so multiple doses often taken
Clinical Effects

• Often indistinguishable from amphetamines
• 1/10 as potent
• Stimulant at lower doses; hallucinogenic at higher doses
• BZP + TMFPP = MDMA like effect
• Palpitations, anxiety, headaches, vomiting
• Seizures 30 min=8 hours post ingestion
• 32% had QT prolongation
Detection/Management

• Often false positives for amphetamine
• GC/MS screens available [but not readily]
• Cardiac monitoring
• IV fluids, cooling, benzos
• Monitor closely
KROKODIL
desomorphine

• Synthetic morphine analog
• Manufactured in the US in 1930
• 10x more potent than morphine
• Fast onset; brief duration of action
Krokodil

• Russia about a decade ago
• Cheap alternative to heroin [1/3 of the cost]
• Made from cooking down desomorphine with gasoline, paint thinner, alcohol, iodine, red phosphorous (match heads), etc.
• Why Russia- no methadone, no clean needles, poverty, high cost of heroin
Krokodil

- Injected
- Destroys tissue
- Turns skin scaly and green, like a crocodile
- Blood poisoning, abscesses, open sores
- Thrombophlebitis/gangrene/amputations/death
- Staph infections/MRSA
- Recent cases in Phoenix
“MOLLY”

- Originally pure powdered form of MDMA
- Now highly adulterated
- Often little MDMA, and more caffeine, meth, methylone etc.
- Popular at concerts; sold for $25-50 a dose
- Frequently seen in ER
- Teeth grinding, dehydration, anxiety, insomnia, loss of appetite and fever
- Uncontrollable seizures, high blood pressure, elevated body temperature and depression
- 2 deaths at a music festival in 2013
Conclusions

• The prevalence of synthetic drugs of abuse is rising
• New substances are becoming available at a rapid rate
• Providers know relatively little about short and long term consequences of these substances
• Better ways of detection, and management are needed