Silent Epidemic: Consequences of Synthetic Drug Use on Psychiatric Outcomes
Learning Objectives

• Explain the epidemiology of synthetic drug use

• Investigate how synthetic drugs may affect the presentation and treatment of mental illness

• Utilize strategies to monitor for and address use of synthetic drugs
A 23-year-old college student with a history of illicit substance abuse is considering trying "bath salts" as a cheap alternative high that won't be detectable in standard drug toxicology screens. A recent study indicates that relative to methamphetamine, the bath salts component, methylenedioxypyrovalerone (MDPV) is likely:

A. 5X less addictive
B. 10X less addictive
C. Equally addictive
D. 5X more addictive
E. 10X more addictive
Peter is a 17-year-old student who has used "spice" several times over the past year. Regarding the long-term adverse effects of synthetic cannabinoid use, there is overwhelming evidence for:

A. Increased risk of psychosis
B. Increased risk of suicidal ideation
C. Increased risk of bipolar disorder
D. All of the above
E. The long-term consequences of synthetic cannabinoid use are relatively unknown
Pretest Question 3

Serena is a 29-year-old mother with a history of major depressive disorder. She reports smoking salvia several times per week because it relieves her depressive symptoms. What is the primary mechanism of action of salvia?

A. Kappa opioid receptor agonism
B. Serotonin 5HT1A partial agonism
C. Serotonin reuptake inhibition
D. Cannabinoid receptor agonism
Designer Drugs

- Marketed as "legal highs"
  - Legal substitutes for cocaine, ecstasy (MDMA), amphetamines, and/or marijuana
- Bath salts
- Synthetic cannabinoids
- Salvia
- Others

CDC. MMWR 2011;60(19):624-7;
Regulation

• October 2011
  – Designer drug components, including several synthetic cannabinoids and the major constituents of bath salts, were categorized as emergency Schedule I substances
    • Temporary (18-month) classification while the US Drug Enforcement Agency (DEA) conducted further studies

• July 2012
  – President Obama signed the Synthetic Drug Abuse Prevention Act
    • Increased the time (from 18 to 36 months) that a substance may be temporarily assigned to Schedule I

Cameron K et al. Psychopharmacology 2013;227(3):493-9;
Regulatory Issues

• Under federal law:
  – Any chemical "substantially similar" to a current Schedule I or II drug can be treated as a Schedule I or II drug if it was developed for the purpose of human consumption and if it possesses the same psychoactive effects as the original compound

• Designer drugs are labeled "not for human consumption" and are camouflaged under names such as "stain remover," "research chemicals," and "insect repellant"

• Active ingredients are a moving target
  – Manufacturers slightly alter the chemical formulas of these drugs
  – When one substance is banned, a new, slightly altered analogue takes its place

Cameron K et al. Psychopharmacology 2013;227(3):493-9;
BATH SALTS
What Are Bath Salts?
What Are Bath Salts?

• Street name for the latest class of designer drug
• Readily available on the Internet and in smoke shops, head shops, and gas stations
  – Sold under a variety of names
  – (See APPENDIX)
• Relatively cheap
  – $20-50 per 50-mg packet
• Labeled "bath salts," "plant food," "pond water cleaner," "novelty collector's items," and "not for human consumption" to circumvent detection and law enforcement

CDC. MMWR 2011;60(19):624-7;
Epidemiology

- Bath salts use became prominent in Europe in 2009
- First reports of bath salts use in the US were in July 2010
- Users are predominantly young (median age: 26) and male (78–84%)
- 26% of bath salts users co-ingest with other substances
  - Opioids (6.2%)
  - Marijuana (5.4%)
  - Alcohol (4.4%)
  - Synthetic cannabinoids (4.4%)

Number of Calls to Poison Control Centers Regarding Bath Salts Exposure

Desired Effects

• Euphoria
• Alertness
• Increased sociability
• Increased empathy
• Intensification of sensory experiences
• Sexual arousal

Adverse Effects

- At least half of users admit to at least 1 adverse event
- Psychotic symptoms are seen in up to 40% of users

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Bath Salts Components

- Methcathinones
  - Synthetic cathinones
    - Natural cathinones are found in the shrub khat (*Catha edulis*), which is chewed or brewed as tea in certain Arabic and African regions
  - Methamphetamine analogues
  - Easily synthesized from ephedrine and pseudoephedrine
  - Mephedrone, methylone, methylenedioxypyrovalerone (MDPV) and/or naphyrone

- Cutting agents include lidocaine, benzocaine, and caffeine

Bath Salts Components

• Contain 1 or more synthetic cathinones
  • Methylone
    – Similar to methylenedioxymethamphetamine (MDMA; ecstasy)
  • Mephedrone
    – Similar to methamphetamine
  • Methyleneedioxyxypyrovalerone (MDPV)
    – Similar to cocaine
• Others include methedrone, flephedrone, and 3-fluoromethcathinone

O'Malley P. Clin Nurse Specialist 2011;25(5):224-5;
## Bath Salts Components

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*DAT: dopamine reuptake transporter*

*NET: norepinephrine reuptake transporter*

*SERT: serotonin reuptake transporter*

Mechanisms of Action

- Cocaine and MDPV inhibit DAT, SERT, and NET
  - Unlike cocaine, MDPV inhibition of DAT does not stop after the drug is taken away

- Methamphetamine, MDMA, mephedrone, and methylone function as DAT and NET substrates, reversing the flow of the transporters

- Mephedrone also acts as an MAOI

- The sum of mephedrone, MDPV, and methylone may be greater than their parts
  - Combination of transporter inhibition along with transporter reversal results in higher monoamine levels than expected from either mechanism alone

Pharmacology

- Pharmacological effects vary depending on purity, concentration, and filler compounds
  - Increased NE
    - Sympathetic effects
  - Increased 5HT
    - Serotonin syndrome
  - Increased DA
    - Reward
    - Addictive potential
    - Transition from recreational to addictive use may occur in a matter of days

Route of Administration and Dosing

• Bath salts may be inhaled, injected, snorted, swallowed, or inserted into the rectum or vagina
• Effects occur with doses of 2–5 mg
• Typical dose range is 5–20 mg
• Effects occur 10–20 min after ingestion
• Desired effects typically last 2–4 hours
• Adverse effects may last 8 hours (or more)
• "Bumping": larger loading dose with several smaller doses every 2–3 hours to maintain the high

Addiction

- Strong urge to re-dose occurs 20–30 minutes after ingestion
- Intranasal dosing produces a more potent high and greater addictive potential than ingestion
- MDPV may be 10X more addictive than methamphetamine (in rats)


# of times a rat will press a lever for a single dose of drug
What To Look For

• Bath salts toxicity may mimic a psychiatric disorder
  – Only 46% of users have a history of mental illness

• Most common signs of bath salts toxicity:
  – Patients are usually disoriented and agitated
  – Dilated pupils with prominent nystagmus (involuntary eye movements)
  – Lockjaw and teeth grinding
  – Rapid, inappropriate, incoherent speech
  – Emotionally, verbally, and physically abusive
  – Elevated liver enzymes and/or liver failure

Detection

- Negative results on standard urine drug toxicology screens
- Specialized labs can detect bath salts components via chromatography-mass spectrometry
  - Results may take several days
  - Bath salts components vary and are constantly tweaked by manufacturers to avoid detection
- Some newer, cheaper urine toxicology assays have recently been developed
  - Screen for 21 designer stimulants

Differential Diagnosis

• Rule out other substances (cocaine, phencyclidine (PCP), lysergic acid diethylamide (LSD), amphetamines, alcohol) using standard toxicology

• Rule out medical and psychiatric conditions
  – Blood chemistries to rule out serum electrolyte imbalances, abnormal glucose levels, and metabolic acidosis
  – Complete blood count to rule out infection or anemias
  – CT scan to rule out subarachnoid hemorrhage or other intracranial pathology
  – ECG will likely demonstrate tachycardia

• Patient admission or witness account of bath salts use

Treatment Is Mainly Supportive

- **Sedatives for anxiety, agitation, aggression, tremors, seizures, and psychosis**
  - Benzodiazepines such as lorazepam or diazepam
  - Several doses may be required
  - Monitor for respiratory depression

- **Antipsychotics as second-line measures**
  - Use with caution due to potential for lowering seizure threshold and potential for worsening hyperthermia by triggering malignant neuroleptic syndrome

- **Physical restraints may be necessary, as bath salts users often display "super human" strength**

Treatment Is Mainly Supportive, cont.

- Beta-adrenergic antagonists (e.g., propranolol) for sympathetic symptoms (e.g., tachycardia, hypertension, palpitations, tremors, sweating, and headaches)
- N-acetylcysteine for hepatotoxicity
- Aggressive intravenous hydration
- Full psychiatric evaluation prior to hospital discharge

Harm Reduction Approach

- Winstock et al. (2010) recommend a harm reduction approach that counsels users to:
  - Avoid regular use to avoid developing tolerance
  - Avoid using bath salts in combination with other stimulants or large amounts of alcohol or other depressants
  - Avoid injecting the drug
  - Remain well hydrated when using the drug
  - Avoid becoming overheated

Long-term Consequences

- Relatively unknown due to lack of long-term studies
- Hepatic and renal failure may occur
- After resolution of psychosis, many patients experience depression and suicidal thoughts
- Patients with underlying psychiatric conditions are at the greatest risk for severe psychiatric reactions
- Possible long-term increased risk of suicide
- Possible increased risk of Parkinsonian-level degeneration
- Evidence of long-term working memory deficits in rats

SYNTHETIC CANNABINOIDS (SPICE)
Epidemiology of Synthetic Cannabinoids

- Also known as "spice," "K2," and "incense"
- From July through November 2010, 35% of samples submitted by juvenile probation departments were positive for synthetic cannabinoids
- 1-year prevalence among 12th graders: 11.4%
  - Second behind marijuana
- 77% of users are male
- Inhalation is the most common route of administration
- $10-20 per gram (usual dose is ~0.3 grams)

Number of Calls to Poison Control Centers Regarding Synthetic Cannabinoids Exposure

Through June 30, 2013

Synthetic Cannabinoids Components

• Designed to mimic the effects of tetrahydrocannabinol (THC)
  – Not derived from the hemp plant (Cannabis sativa)

• Constituents and dosages can vary greatly between products and lots and even within the same package

• Synthesized in labs and formulated to interact with endogenous cannabinoid receptors
  – Over 400 synthetic cannabinoids originally developed for potential therapeutic applications (nausea, pain, etc.)

Mechanism of Action

• Decrease GABA levels
• Increase glutamate and dopamine levels
• In addition to direct modulation of serotonin release by GABA, serotonin levels can also be affected indirectly by endocannabinoid control of GABA and glutamate release.

### Synthetic Cannabinoids Carry a Higher Risk of Causing Psychosis

#### Marijuana
- Contains cannabidiol, which is thought to have antipsychotic properties
- Partial agonist at the cannabinoid 1 (CB-1) receptor

![THC molecule](image)

#### Synthetic Cannabinoids
- Do not contain cannabidiol
- Full agonists at the CB-1 receptor
- Bind CB-1 receptors with up to 800X greater affinity

![HU-210 molecule](image)

What To Look For

- Agitation
- Alteration of time perception
- Anxiety
- Depression
- Dysphoria
- Elevated blood pressure
- Listlessness
- Hallucinations
- Nausea
  - Severity may differentiate spice from marijuana use
- Paranoia
- Seizures
- Suicidal thoughts
  - Reported by as many as 40% of users
- Tachycardia

Symptoms typically last up to 6 hrs

Detection and Treatment

• Commercial testing is available to detect synthetic cannabinoid metabolites
  – Formulations change so often that most tests quickly become obsolete

• Spice intoxication should be suspected in any patient presenting with bizarre behavior, anxiety, agitation, and/or psychosis who has no known psychiatric history

• Intravenous benzodiazepines are most commonly used for agitation and seizures

Long-term Consequences

- Relatively unknown due to lack of long-term studies; much speculation based on consequences of heavy marijuana use
- Spice use may cause recurrence or exacerbation of pre-existing psychotic symptoms
  - Possible 3X increased risk of subsequent psychosis
  - 30% of users have persistent psychosis at 8-month follow-up
- Depression and suicidal ideation may persist
- Reduced hippocampal and amygdala volumes
  - Alterations in emotional processing and cognitive functioning
- Kidney failure has been reported in several cases
- Dependence and withdrawal have also been reported

SALVIA
Epidemiology of Salvia

- Also known as "Diviner's Sage," "Mystic Sage," "Maria Pastora," "Magic Mint," and "Purple Sticky"

- Used by Mazatec shamans in Central America for religious and medicinal purposes for centuries

- Used as a legal psychoactive narcotic since the mid-1990s in Europe and the US

- A 2011 survey showed that 5.9% of high school seniors had used salvia in the past 12 months

- $10/gram

- Not detected in standard drug screens

- Currently, no federal law prohibits the possession or use of salvia
  - Available online and in head shops

Pharmacology and Mechanism of Action of Salvia

- Salvia comes from *Salvia divinorum*, an herb and a member of the mint family
- Salvinorin A is the psychoactive chemical found in salvia
  - Most potent natural hallucinogen known
  - Selective and potent kappa opioid agonist
- Salvia leaves are smoked or ingested
  - Onset of hallucinogenic effects: within 30 seconds
  - Effects last for 30 minutes to 3 hours
  - Hallucinogenic activity with as little as 200 μg
- Relatively low addiction potential
- May have antidepressant effects

Desired Effects

Psychedelic properties similar to lysergic acid diethylamide (LSD)

- Relaxation and improved mood
- Intense psychedelic effects
- Altered state of consciousness
- Vivid visual hallucinations
- Auditory hallucinations
- Dream-like experience
- Floating feeling
- Spiritual experience
- Feelings of dissociation
- Increase in sensual and aesthetic appreciation
- Synesthesia
  - Stimulation of one sensory pathway causes automatic stimulation of a second sensory pathway
- Increased self-confidence
- Increased insight

Adverse Effects

- Loss of control over experience
- Difficulty integrating experiences
- Racing thoughts
- Sleepiness and physical exhaustion
- Dizziness
- Irritability
- Anxiety

- Dysphoria
- Psychosis
- Psychomotor agitation
- Language impairment
- Amnesia
- Lack of motor coordination
- Excessive sweating
- Chills
- Nausea and vomiting

Long-term effects are relatively unknown

Summary

- Designer drugs, such as bath salts, spice, and salvia, have grown in popularity due to their representation as legal alternatives to illicit substances and their limited detection by standard drug toxicology screens.

- Designer drug users may present with symptoms that resemble psychiatric disorders, including schizophrenia, anxiety disorders, and depression.

- Given the recent emergence of designer drugs, the long-term consequences of their use has not been extensively studied and is relatively unknown.

- Clinicians should consider designer drug use in the differential diagnosis of patients who present with psychiatric symptoms, especially if there is no medical record for an existing psychiatric diagnosis.
### APPENDIX: Various Bath Salts

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APPENDIX: Various Bath Salts

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- Meth's Kitten
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- Mint Mania
- MMC Hammer
- Moonshine
- Mr. Nice Guy
- Mystic
- NRG-1
- Ocean Burst
- Ocean Snow
- Oceanic Deeper
- Piercing
- Piko
- Plant Food
- Pure Ivory
- Purple Rain
- Purple Tranquility
- Purple Wave
- Raka
- Rave On
- Raving Dragon
- Recharge
- Red Dove
- Red Sky
- Rocket Fuel
- Ronzio
- Route 69
- Rush
- Russian River
- Scarface
- Sextacy
- Silverback Bath Salts
- Snow Blow XXX
- Snow Day
- Snow Leopard
- Special Diamond
- Special Gold
- Special Original
- Speed Freak
- Spice E
- Stardust
- Stroof
- Subcoca
- Summer Daze
- Sunshine
- Torsk
- Tranquility
- Vanilla Sky
- Volt
- Wannabe-Speed
- Whack
- White Aroma Crystals
- White China
- White Dove
- White Girls
- White Gold
- White Horse
- White Knight
- White Lightning
- White Rush
- White Snow
- Wicked X
- Wicked XX
- Wild Cat
- Wild Cat Oceanic Charge +
- Xtacy
- Xtreme
- Zeus 2
- Zoom
- Zoom 2
- Zsu-Zsi