Disclosure

• I have no financial relationships with any commercial interest related to the content of this presentation

• Legal review

• ECN reviews
Objectives

1. Cite the novel psychoactive substances and describe how to recognize the use of these drugs in clinical practice.

2. Describe the common symptoms of novel psychoactive substances and complications that are encountered.

3. Describe the current management of an acute toxic event suspected or known to be due to novel psychoactive substances.
Novel Psychoactive Substances

- Unprecedented Proliferation
- Europe: 41 new psychoactive substances identified in 2010
- Majority: Synthetic
  - Cannabinoids
  - Amphetamine like stimulants
  - Opioid-like substances
  - Hallucinogens
Analysis of anonymous pooled urine from portable urinals in central London confirms the significant use of novel psychoactive substances

J.R.H. ARCHER¹, P.I. DARGAN¹,², S. HUDSON³ and D.M. WOOD¹,²

From the ¹Clinical Toxicology, Guy’s and St Thomas’ NHS Foundation Trust and King’s Health Partners, Westminster Bridge Road, London, SE1 7EH, ²King’s College London, Strand, London, WC2R 2LS and ³HfL Sport Science, LGC Health Science, Newmarket Road, London, CB7 5WW, UK
Patient Presentation

- 1/18/13 0039
- Oconee Regional Medical Center
- 19 yom
- “300 mg MXE”
- Pt is unresponsive, no gag reflex pinpoint pupils.
- Pt was given 2mg of narcan-no response.
- Seizure Activity, pt intubated.
- EKG=wnl. Skin warm and dry.
- Vitals: P-89, BP-143/87, RR-14 O₂ sat 100%
- ASA/APA neg, Ethanol 128, CMP WNL
Outcome

- Extubated at 1700, recovered
- HR 63 117/73 afebrile FiO2 45%,
- Neurology eval for new onset seizure,
- Agreed to go to outpatient rehab
Methoxetamine (MXE)

- 3-MeO-2-Oxo-PCE
- Ketamine derivative
- Rational drug design: its N-ethyl group was chosen to increase potency.
- Ketamine is a non-competitive NMDA receptor antagonist
- Also binds to opioid mu and sigma receptors at high doses.

Methoxetamine has a 3-methoxy group instead of 2-chloro group on the phenyl ring of ketamine and an n-ethyl group instead of the n-methyl group on the amine portion of the molecule.
Methoxetamine

- First identified in November 2010.
- July 2011,
  - Sold on 58 websites
  - 145–195 euros for 10 grams.
- Sold as a stand alone fish tank cleaner and can be found over-the-counter in many stores across the UK and US.

- Methoxetamine’s effects are described by some as similar to ketamine or high-dose DXM, while others report not finding it similar to those substances. A number of accounts describe compulsive redosing and unintentional consumption of more than was initially planned.
Ketamine & Methoxetamine

- In overdose, the most common effects are sedation and respiratory depression.
- Tachycardia, HTN palpitations and chest pain.
- Nausea, vomiting, diarrhea

Nervous System
- Seizures (rare)
- Respiratory Arrest
- Perceptual distortions, dissociative/catatonic states, hallucinations, paranoia, agitation, memory loss, slurred speech, cerebellum toxicity and rotatory nystagmus.
Cannabinoids are a class of diverse chemical that activate cannabinoids receptors.

- Endocannabinoids
- Phytocannabinoids
- Synthetic cannabinoids
Synthetic Cannabinoids

- Legit research seeking cannabinoid receptor agonist with analgesic and anti-inflammatory effects without the psychotropic effects
- 7 major groups: Hundreds developed
- Mixed with variety of herbs
Some Brand Names

- Spice, K2
- Chill zone cherry
- Chaos mint
- Tai fun blackberry
- Smoke
- Clover Spring
- Aztec thunder
- Exclusive Sensation
- Zen
- Sensation vanilla
- Natures organic truskawka (strawberry)
Synthetic Cannabinoids

- CB₁ & CB₂ receptor agonist
- Higher binding affinity than Δ⁹-THC
- Full agonists
Clinical Effects

- Anxiety
- Paranoia
- Agitation
- Delusions
- Tachycardia
- Diaphoresis
- Conjunctival Injection
- Xerostomia
- Cycling Vomiting
- Pulmonary Infiltrates
- AKI
- Possible Withdrawal symptoms
Detection

- Do not cross react with current Δ9-THC immunoassays
- Commercial assays
- Can be detected with GC/MS or LC/MS
- Persistence Unknown
In the US, as of March 1, 2011, five cannabinoids, JWH-018, JWH-073, JWH-200, CP-47,497, Cannabicycldhexanol were made Schedule I.

Synthetic Drug Abuse Prevention Act of 2012
Treatment

- BZD for agitation
- Supportive
- Observation until resolution, most a few hours
Phenethylamines

1: A naturally occurring compound found in both the animal and plant kingdoms. It is an endogenous component of the human brain.

2: Any of a series of compounds containing the phenethylamine skeleton, and modified by chemical constituents at appropriate positions in the molecule.
Phenethylamines (2Cs)

Epinephrine  Norepinephrine  Dopamine  Serotonin
Brain Neurotransmitters

- **Epinephrine**: Increased heart rate
- **Norepinephrine**: Increased blood pressure, Alertness, Concentration
- **Dopamine**: Entactogenic effects, Locomotor effects, Pleasure, Reward
- **Serotonin**: Entactogenic effects, Hallucinations, Compulsion / addiction, Seizures
Phenethylamines I Have Known And Loved
Adding alkyl chains at the α position:
1. Increases lipophilicity (BBB penetration)
2. Inhibits MAO breakdown
3. Potentiates hallucinogenic properties
Amphetamines

Methamphetamine

Adding n-substitutions:
1. Decreases sympathomimetic effects
2. Increases lipophilicity
3. Increases duration of action

10 Years of Meth Use
Phenethylamines

Phenyl ring substitutions:
1. Halogenating position 4 = ↑ hallucinogenic properties
2. Substitutions at 2,4,5 maximize 5-HT\textsubscript{2A} effects
3. Methoxy substituitions ↑ serotonergic effects
Phenethylamines

Phenyl ring substitutions:
1. Halogenating position 4 = ↑ hallucinogenic properties
2. Substitutions at 2,4,5 maximize 5-HT\textsubscript{2A} effects
3. Methoxyxy substitutions ↑ serotonergic effects
4. Mescaline or 3,4,5-trimethoxyphenethylamine
Phenethylamines

Entactogens

Methylenedioxymethamphetamine
MDMA (Ecstasy)
Serotonin

Methoxy substitutions:
1. Very potent serotonergic properties
2. Intense entactogenic effects
Marijuana
Cocaine
Cathinones

Cathanones

Bath salts are not made from Khat.

Catha edulis

Cathinone
Synthetic Cathinones

Mephedrone

MDPV

Bupropion

H

Cl
Synthetic Cathinones

Mephedrone

\[
\begin{align*}
\text{Mephedrone} & : \quad \text{H}_3\text{C} - \text{CH}_3 & \quad \text{CH}_3 - \text{CH}_3 \\
\text{Methylylone} & : \quad \text{O} - \text{C} - \text{N} - \text{CH}_3 \\
\text{MDPV} & : \quad \text{O} - \text{C} - \text{N} - \text{CH}_3
\end{align*}
\]

Bath Salt Exposures per Day

DEA Emergency Schedule I
Synthetic Cathinones
What’s in Bath Salts:
1. 9 different compounds
2. 5 mg to > 1 g
<table>
<thead>
<tr>
<th>Route</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufflation</td>
<td>10-20 min</td>
<td>1-2 hrs</td>
</tr>
<tr>
<td>Ingestion</td>
<td>15-45 min</td>
<td>2-4 hrs</td>
</tr>
<tr>
<td>Intravenous</td>
<td>10-15 min</td>
<td>30 min</td>
</tr>
</tbody>
</table>
Synthetic Cathinones

Clinical Effects:

• Sympathomimetic toxidrome
  – Tachycardia, hypertension, hyperthermia

• Agitation (82%), Violent-combative (57%), Hallucinations (40%)
  – one death from self-injury

• Seizures
  – One death from status epilepticus

• Hyponatremia (118-125 mEq/L)
  – Two deaths from cerebral edema
Synthetic Cathinones

285. Fatalities following parenteral injection of MDPV sold as “hookah cleaner”
Ronald I. Kirschner², Henry C. Nipper¹, Patricia K. Studts³, Kathy L. Jacobitz⁴
¹Creighton University Medical Center, Omaha NE USA; ²University of Nebraska Medical Center, Omaha NE USA; ³Creighton Medical Laboratories, Omaha NE USA; ⁴Nebraska Regional Poison Center, Omaha NE USA

288. Psychosis from a bath salt product containing flephedrone and MDPV with serum, urine, and product quantification
Stephen L. Thornton¹, Roy R. Gerona², Christian A. Tomaszewski¹
¹University of California – San Diego, San Diego CA USA; ²University of California – San Francisco, San Francisco CA USA

290. Clinical presentations and medical complications after exposure to substances labeled as “bath salts”: A ToxIC preliminary report
Blake A. Froberg⁴, Michael Levine¹, Kristin M. Engebretsen², Nathanael J. McKeown⁵, Mark Kostic⁶, Christopher D. Rosenbaum³, Daniel E. Rusyniak⁴

Tachycardia (70%)
Hypertension (35%)
Hyperthermia (15%)
Acidemia (37.5%)
Hypokalemia (27.5%)
293. Comparison of synthetic cathinone and methylenedioxymethamphetamine (MDMA) exposures

Mathias B. Forrester¹, Liza Leung², Kurt Kleinschmidt²

¹Department of State Health Services, Austin TX USA; ²University of Texas Southwestern, Dallas TX USA

Table 1. Results for abstract 293.

<table>
<thead>
<tr>
<th></th>
<th>Synthetic cathinones (%)</th>
<th>MDMA (%)</th>
<th>RR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>45.5</td>
<td>27.2</td>
<td>1.67, 1.3–2.1</td>
</tr>
<tr>
<td>Agitation</td>
<td>37.3</td>
<td>18.1</td>
<td>2.06, 1.53–2.77</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19.2</td>
<td>9.4</td>
<td>2.03, 1.30–3.16</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>17.8</td>
<td>9.4</td>
<td>1.88, 1.20–2.95</td>
</tr>
<tr>
<td>Confusion</td>
<td>12.3</td>
<td>3.0</td>
<td>4.10, 1.93–8.62</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9.4</td>
<td>4.1</td>
<td>2.30, 1.18–4.48</td>
</tr>
<tr>
<td>Chest pain</td>
<td>7.5</td>
<td>7.9</td>
<td>1.05, 0.59–1.87</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6.8</td>
<td>2.7</td>
<td>2.48, 1.1–5.6</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6.4</td>
<td>2.7</td>
<td>2.34, 1.03–5.34</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV fluids</td>
<td>50.0</td>
<td>34.0</td>
<td>1.47, 1.2–1.8</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>38.4</td>
<td>21.5</td>
<td>1.78, 1.35–2.34</td>
</tr>
<tr>
<td>Oxygen</td>
<td>9.6</td>
<td>4.2</td>
<td>2.31, 1.17–4.54</td>
</tr>
<tr>
<td>Other sedation</td>
<td>6.8</td>
<td>1.9</td>
<td>3.63, 1.38–9.53</td>
</tr>
</tbody>
</table>
Testing for Cathinones

Designer Stimulants Testing
MDPV, Mephedrone and Methylene
("Bath Salts")

Routine drug tests do not detect the synthetic stimulants found in "bath salts" and "plant food." NMS Labs now offers **quantitative** testing for these key ingredients - MDPV, Mephedrone and Methylene.

**Mephedrone, MDPV and Methylene**

Called "bath salts" or "plant food" by illicit drug users and makers, these designer drugs are dangerous stimulants and hallucinogens. Although labeled as "not for human consumption," these substances often come in pill or powder form and are snorted, injected or smoked by users.
NBOMe

- N – benzyl substitution with OMe groups on the ring
- Discovered in 2003
- Initially surfaced in Russia
- Currently unscheduled*
- NBOMe

- Not a homogenous group

- Potent 5-HT$_{2A}$ agonists

- 25I, 2C-I, 2C-B, 2C-C compounds
NBOMe

Clinical Effects:

- Sympathomimetic toxidrome
  - Tachycardia >> hypertension
- Hallucinations / agitation
- Seizures
Tachycardia (90%)
Hypertension (70%)
Agitation (60%)

Hallucinations (50%)
Seizures (20%)
1. High affinity for 5-HT receptors
2. Potent hallucinogens
3. Potent vasoconstrictors
Clinical Effects:

• Slow Onset, long duration
• Sympathomimetic toxidrome
  – Tachycardia, hypertension, hyperthermia
• Severe vasoconstriction
  – Delayed effects
• 5 deaths in Sweden
Bromo-Dragonfly Death and Hospitalization in Sweden

by Erowid, Suave, and Abrahad

v1.0 Aug 16, 2008
Management

Benzos, Benzos, Benzos
### Pharmacokinetics of Benzos

<table>
<thead>
<tr>
<th></th>
<th>Diazepam</th>
<th>Midazolam</th>
<th>Lorazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action (IV)</td>
<td>Rapid</td>
<td>Rapid</td>
<td>Rapid</td>
</tr>
<tr>
<td>Duration of action</td>
<td>1-2 hr</td>
<td>30-80 min</td>
<td>2-4 hr</td>
</tr>
<tr>
<td>T peak CSF conc</td>
<td>3.7 min</td>
<td>3.7 min</td>
<td>7.0 min</td>
</tr>
<tr>
<td>T EEG Δ</td>
<td>0.89 min</td>
<td>0.29 min</td>
<td>3.8 min</td>
</tr>
<tr>
<td>Duration EEG Δ</td>
<td>7.5 min</td>
<td>6.3 min</td>
<td>28.3 min</td>
</tr>
<tr>
<td>Active metabolite</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Management

- Benzos, Benzos, Benzos
- Aggressive cooling
- Control seizures
- Look for rhabdomyolysis
- Look for serotonin syndrome
Summary

- Cathinones = Sympathomimetic + serotonin (agitation, hallucinations)
- NBOMe = Cathinones w/ ↑ tachycardia and seizures
- BromoDragonFly = Cathinones w/ vasoconstriction
- Benzos, Benzos, Benzos + call Poison Control
Kratom Trees – Mitragyna Speciosa
Kratom

- Native to SE Asia
- Used for centuries
- Stimulate (NE, 5-HT) and Analgesic properties (Mu, Delta)
Kratom

- Leaves chewed, smoked or drink as tea
- 2-6 grams: "therapeutic" use include mild euphoria and CNS stimulation
- > 6 grams: stupor, vertigo, rombergism, nausea and vomiting, rare seizure
- Duration 4-6 hours
- Chronic use can produce skin discoloration, anorexia, weight loss, addiction and withdrawal
Kratom

• Not regulated by the United States federal government.
• DEA includes the botanical in its "Drug and Chemical of Concern" list.
• It is sold online, in “tobacco or head shops” throughout the country as raw or crushed leaves that can be put into empty capsules, made into tea, eaten, or smoked.
Salvia Divinorum

- Oaxaca, Mexico
- Mazatec Indians
- Intense very short-term hallucinogenic experience
Salvia Divinorum

- Route
- Rapid onset
- Duration 5 minutes-2 hours
Salvia Divinorum

- Synesthesia
- Uncontrollable laughter
- Past memories, such as revisiting places from childhood memory
- Sensations of motion, or being pulled or twisted by forces
- Merging with or becoming objects
- Overlapping realities: perception of being in several locations at once
Desomorphine
Krocodile

- Invented in 1932
- Derivative of Morphine; 8-10 x
- 2010 outbreak in Russia
Thionyl chloride

Codeine → a-Chlorocodide → Desocodeine → Desomorphine

catalytic reduction

Demethylation
Krocodile

- Codeine availability
- 30-60 minutes to prepare with over-the-counter ingredients
- Similar to Heroin, shorter duration
- Many impurities
- Severe Tissue Damage
- Life span 2-3 years
Questions?