From K2 to Kratom
Update on Novel Drugs of Abuse

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Disclosures
- No personal disclosures
- No personal experience with experimentation
- Will be discussing for the entire talk
  - Drugs of abuse which are non-FDA approved.
  - Drug misuse outside of the FDA approved indications

Novel Drugs of Abuse
- Sympathomimetics
  - “New” Designer amphetamines
  - Synthetic cannabinoids
- Dissociative agents
- Hallucinogens
  - “herbals”
- Opioids
My New Year’s Eve

- 17 year old male, presents to the Peds ED from Bassnectar concert
  - Very agitated, diaphoretic
  - Pulse 140’s, BP 160/100, Resp rate 24
  - Yelling, screaming
  - Missing vital sign??
    * Temp 106°

Initial approach

- Differential?
  - Sympathomimetics
- Airway management as needed
- Evaporative cooling
  - Wet and Windy
- Hydration
- Benzo’s-How much?
  - Enough!

Old School Phenyalkylamines

- Amphetamines
- Methamphetamines
  - Crystal meth
  - Crank
  - Ice
Adolescent drug abuse, 1990s

Amphetamine structures
“Designer” Phenylalkylamines

Structure modification of the amphetamine structure yields more serotonergic and hallucinogenic effects.

“Pharming”, 2000s

- ADHD drugs
  - Ritalin (methylphenidate), Vyvanse (lisdexamfetamine), Adderall (amphetamine, dextroamphetamine)
  - “Trail mix”, “Bowel parties” “BYOB” (medicine bottle, not liquor bottle)
Bath Salts: Not your Bed, Bath, and Beyond

Molly’s Plant food: Only for “adult” plants
- Ivory Wave
- Ocean Burst
- Cloud 9
- White Lightning
- Scarface
- White Dove
- Pure Ivory
- Snow Leopard
- Sextasy
- Vanilla Sky
- Hurricane Charlie

Synthetic cathinones
- First recognized in US markets in 2008-9 and then use exploded
- Recent report by Texas Poison Centers
  - Age range of adolescents: 12-19
  - Exposure by inhalation 66%
  - Exposure reportedly occurred in patient’s own residence

PEC 2013-29-151-5

Synthetic cathinones
- Designer drugs that are synthetic derivatives of khat (*Catha edulis*)
  - Native to Ethiopia, cultivated in East Africa
  - Fresh leaves are wrapped in banana leaves and shipped to other countries
  - Contain cathinone
  - Typically chewed
Synthetic cathinones

- Designer drugs are synthetic derivatives of khat (*Catha edulis*)
  - Mephedrone (miaow-miaow, MCAT)
  - 3,4 methylenedioxypyrovalerone (MDPV)
  - METHyleone
  - Methcathinone
  - Methedrone

Synthetic cathinones

- Intoxication
  - Sympathomimetic-PCP like effects
  - Reports of acute paranoid psychosis, self mutilation, mood changes
  - Myocardial infarction and myocarditis reported

Observational study-registry of consecutive adult patients who presented with acute coronary syndrome

- Higher rates of heart failure, recurrent ischemia, re-infarction, cardiogenic shock, and stroke in Khat users with ACS.

*Circulation* 2011
Khat

Contributing vasospasm or hypercoagulability
*Circulation, 2011*

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**Hallucinogenic amines**
Synthetic phenylethylamines

![Mescaline](image)

!["BOD"](image)

!["2CI"](image)

*Peyote cactus*

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**Hallucinogenic amines**

- "2C" drugs
  - 2 carbons between amino group and benzene ring
  - Agonists at 5HT₂ receptor
  - 2CI blocks reuptake of dopamine, serotonin, and norepi
  - Agonist at alpha, receptor

*JMT 2013*
Hallucinogenic amines

- 2C-I: Smiles, Mr. Nice Guy, Infinity, Isabel, Izzy
- 2C-E: Eternity, Bleach, Tootsie, Rockets, Double Dunters

19 yr old male insufflated “liquid acid”
- Seizures, agitation, diffuse LE rigidity with clonus. BP 230/104
- Temp peaked at 40.3 by HD 2

Internet is a dangerous resource
### PiHKAL
**Phenylethylamines I Have Known and Loved**
Published in 1991

Amazon price:
- Paperback
  - $20.92

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<th>Compound Name</th>
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<td>BOB  4-Bromo-2,5,beta-trimethoxy-PEA</td>
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<td>14</td>
<td>BOD  2,5,beta-Trimethoxy-4-methyl-PEA</td>
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<td>17</td>
<td>BOM  3,4,5,beta-Tetramethoxy-PEA</td>
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</tbody>
</table>

### TiHKAL
**Tryptamines I have known and loved**

- Synthesis manual for over 55 psychedelics
- Amazon price: $20.92
- "Frequently bought together": PiHKAL, TiHKAL, The Shulgin index
  - $100.77
No money, No problem

- Vaults of Erowid
- Online versions of the PiHKAL and TiHKAL

`#26. LSD-25
ACID; LYSERGIDE; D-LYSERGIC
ACID DIETHYLAMIDE; METH-LAD;
D-LYSERGAMIDE, N,N-DIETHYL;
N,N-DIETHYL-D-LYSERGAMIDE;
9,10-DIDHYDROX-N,N-DIETHYL-6-
METHYLERGOLINE-8b-
CARBOXAMIDE`

Monster weed
K2, Spice

Photos courtesy of
Dr. John G. Benitez

A story that started at Clemson

- John W. Huffman-researched the interaction between drugs and brain receptors.
- Worked on ligands for the cannabinoid receptors.
- The chemical compounds Huffman developed have been made into synthetic marijuana that is marketed as "Spice," "K-2," "Skunk" and similar products.
A story that started at Clemson

- Huffman says that although he is not surprised that people are smoking the compounds to get high,
  “We never intended them for human consumption.”

Synthetic cannabinoids

- THC
- JWH-073

- Sprayed onto plant material
  - Herbal (hence the name “spice”)
- Plant material is then smoked or vaporized to enhance uptake
Synthetic cannabinoids

- First recognition of substances in US around 2008. DEA made commonly used ones Schedule 1 in March 2011.
- Monitoring the Future survey of youth:
  - 2011: 11.4% of 12th graders had used synthetic cannabinoids.
  - 2012: 11.3% for 12th graders, 8.8% for 10th graders, and 4.4% for 8th graders


The DAWN Report

Synthetic cannabinoids

- Bind variably to CB1 and CB2 receptors with higher affinity than marijuana
  - CB1 CNS – primary pharmacologic effects from cannabinoids
  - CB2 periphery
Synthetic cannabinoids

- Manifestations
  - Paranoia/anxiety/psychosis
  - Hallucinations
  - Vomiting
  - Tremors/seizures
  - Tachycardia, Hypertension
- Duration: up to several hours
Synthetic cannabinoids
Acute kidney injury

26 yr old who smoked “Mr. Happy”
Creatinine 5.38 mg/dL
Analysis: XLR-11, UR-144, metabolites

14 patients in multiple states
Ages 15-33, 12 were males
Cr range 3.3-21 mg/dL
Of those tested: XLR-11 metabolite

Synthetic cannabinoids
Stroke

A case of subcortical ischemic following injection of a synthetic cannabinoid

22 yr old male brings his dog to the vet for convulsive activity. While the dog was being evaluated, the owner started having seizures and was taken to the hospital. Pt had second admission to the hospital 3 months later for same illness. Lab confirmed PB-22 in the canine and human.

Not just toxic to humans

‘Crazy Monkey’ Poison Man and Dog: Human and canine seizures due to PB-22, a novel synthetic cannabinoid

22 yr old male brings his dog to the vet for convulsive activity. While the dog was being evaluated, the owner started having seizures and was taken to the hospital. Pt had second admission to the hospital 3 months later for same illness. Lab confirmed PB-22 in the canine and human.
“Vaporizers”

Management

- Supportive like other sympathomimetics
- Detection by urine drug screens?
  - NOT

Cocaine

- Rapid absorption following all routes of exposure
- Metabolized through enzymatic and non enzymatic pathways
- Half-life: 0.5-1.5 hours
- Duration of effects: 30-120 minutes
Cocaine

- Blocks reuptake of catecholamines
  - Adrenergic effects
  - Vasoconstriction
- Increases excitatory amino acid concentrations in brain
- Blocks sodium channels

Cocaine + Cocktails

- Formed from the transesterification of cocaine in the presence of ethanol via carboxylesterase

After Sodium Bicarbonate
Cocaine + Cocktails

Cocaine + EtOH = Cocaethylene (CE)
- CE → sodium channel blocking effects, myocardial depression correlates with level
- CE has longer half-life than cocaine so clinical effects may persist longer than expected
- Less of a high, but lasts longer

Cocaine

Synthetic derivatives
- Dimethocaine (larocaine)
  - Half the potency of cocaine
  - Induces tachycardia, ?respiratory arrest
  - Sometimes marketed as a bath salt
- 4-fluorotropacocaine
  - About a third the potency of cocaine
  - Also sometimes combined in bath salts

Cocaine, et al

- Be wary of patient with + cocaine screen and +BAL
- “Bath salts” may be synthetic cocaine derivatives
- “Legal” cocaine may be synthetic cathinones.
Case

21 yr old male brought by EMS
- Using a “white powder”
- Appears to be in a “different world”
- Tachycardic and slightly hypertensive
- +rotary nystagmus
- Moans “Special K” (Not Kellogg)

Ketamine
Special K, vitamin K, cat valium, jet
- Usually use powder form for ingestion or insufflation
- Clinical manifestations: Dissociative effects (K-hole), mild sympathomimetic effects, increased secretions
- Issues:
  - Emergence phenomena
  - Bladder toxicity (incontinence, cystitis, injury to bladder cells)

Methoxetamine
Special M, Kmax, Mexxy
- Congener of ketamine
- Routes: Oral, insufflation, IM, PR, IV
- Can be purchased on internet
  - Tox Fellow at a PC ordered some on internet
  - 500mg for $62 US dollars
Methoxetamine

- Longer duration of action: 5-7 hours
- Similar pharmacodynamics as ketamine
  - More vivid hallucinations
  - Acute cerebellar toxicity
  - Psychomotor agitation
  - More "bladder friendly than ketamine

Even the military is concerned

- The Ketamine Analog Methoxetamine: A New Designer Drug to Threaten Military Readiness
  Mil Med 2014;179:1149-57

Peds ED

- 14 yr old brought in for hallucinations
  - Tachycardic
  - Mydriasis
  - Not agitated
  - Clearly hallucinating
  - Differential?
Hallucinogens

- LSD analogues
  - Stimulate 5HT$_2$ and dopaminergic receptors
  - Effects: 6-12 hours
  - Patients who present for care
    - Used in combination with something else (knowingly or unknowingly)
    - Unexpected user
    - Trauma!!!!

Psilocybin

- *Psilocybe spp.*
- *Conocybe cyanopus*
- *Panaeolus foenisecii*
- *Gymnopilus spectabilis*
- *Psathyrella foenisecii*

But he was at Youth Group!

- “Natural” substances are becoming more popular
- Ask about eating seeds.
“Natural” hallucinogens
Anticholinergics

Before

After

“Natural” hallucinogens

- Morning glory seeds
  - May start with 25-50 seeds, typical dose is 100-400 seeds
  - Lasts 6-10 hrs
- Hawaiian baby woodrose
  - May start with 1-4 seeds with 12+ giving a heavy high
  - Lasts 5-8 hrs

Reversal with physostigmine
“Natural” hallucinogens

- Nutmeg (*Myristica fragrans*)
  - Myristicin
  - Aromatics in nutmeg are metabolized to amphetamine-like cmpds
  - Weak MAO inhibitor activity
  - Serotonergic activity
  - Dose: 5-30 gm for average adult
    - 5-7 gm = 1Tbsp

“Natural” hallucinogens

Nutmeg

- Onset: delayed a few hrs after ingestion
- Duration: about 24 hrs
- Effects:
  - Hallucinogenic, euphoria
  - Lots of nausea, vomiting, tachycardia and even hypotension

What do these have in common?

- Magic mint
- Psychedelic sage
- Mazatec Indians
- Miley Cyrus
Salvia divinorum

- Latin *salvere*-to feel well and healthy
- Usually smoked but can chew leaves
- Cross sectional study of Canadian adolescents
  - 3.8% using Salvia in last year
  - 6.2% used in lifetime
  - Higher use than cocaine/amphetamines
  - Lower use than XTC, cannabis, hallucinogens
  - Of Cannabis users, 23.5% had used Salvia

Drug and Alcohol Dependence 128:166-70; 2013

Salvia divinorum

- Salvinorin A: agonist at Kappa opioid receptor

“Salvia scale”

- Subtle effects
- Altered perception
- Light visionary state
- Vivid visionary state
- Immaterial existence
- Amnesiac effects

Peds ED

- 17 yr brought by dad for detox
  - Mild withdrawal symptoms
  - Has been using opioids and will “use anything he can get his hands on”
  - Prefers roxies, oxycontins, but will take lortabs, norco in a pinch. Prefers to snort the drugs.
Opioids

- Huge issue with diversion
- Rise in heroin and other illicit forms of opioids as there is less availability of “prescription” drugs for diversion?
- Oxycodone
  - Oxycodone: Purdue added sticky gelcoat over tabs
  - “Roxies” - no coating, no time release

Opana

- Oxymorphone HCl
- Street names: Blues, octagons, pink lady, biscuits
- Approved in 2006, later reformulated as “crush resistant” - but still being crushed for injection

Morbidity and Mortality Weekly Report

- Acetyl Fentanyl Overdose Fatalities — Rhode Island, March–May 2013
  - An unusual pattern of toxicology results among 10 OD deaths of suspected illicit drug users.
  - ELISA of blood samples was positive for fentanyl in all 10 cases, but GC/MS did not detect fentanyl.
  - The mass spectrum was consistent with acetyl fentanyl.
DHHS Issues Health Advisory for Deadly New Synthetic Drug

Acetyl Fentanyl Detected in Specimens Associated With Three N.C. Deaths This Year
For Immediate Release
Wednesday, February 19, 2014

- Synthetic analog
  - more potent than heroin (5-15X)
  - less potent than fentanyl
- 50 confirmed deaths in PA after testing started in 2013
- Appearance in TX
- Laced in the heroin?

Acetyl fentanyl

- Large doses of naloxone required.
- Detection
  - Not detected by typical opiate screens (similar to fentanyl)
  - ELISA might be positive for fentanyl—but GCMS shows acetyl fentanyl.
Mr. Smiley

- “Relaxation shots”
- Sold in smoke shops
- Other names: VivaZen, KXL Liquid, Kratom, Kratom Shots, Mr. Smiley, Euphoria, Part Shots

“Natural” treatment for opioid withdrawal

- Kratom: *Mitragyna speciosa*
  - Native to swampy areas of Asia and Africa
  - Available on internet (obviously without prescription)
  - $10-$40 per ounce of plant material
  - Can be chewed, smoked, or brewed as a tea

Kratom

- Mitragynine is structurally distinct from opiates
  - Active at opioid delta and mu receptors
- Animal models: stimulates alpha2 and blocks 5-HT2A receptors
Kratom

- Dose dependent effects: duration of 2-6 hrs
  - Low dose: stimulant
  - High dose: opioid effect
- Uses
  - reduce opioid withdrawal symptoms and for chronic pain
  - low and high doses may be used for euphoric effects

In TN, the plant and active component hydroxymitragynine is a Schedule I Drug as of July 1, 2013.

The drug is legal in most of the US, is on the DEA list of Drugs and Chemicals of Concern.

Opioid management

- Naloxone-May need high doses
  - Counteract affinity of drug for receptor
  - Need large amt of antagonist for large amt of drug
- Monitor for noncardiogenic pulmonary edema if person is “found down” and then becomes hypoxemic
Summary

- Novel drugs of abuse
  - Many derived from “natural” products or modifications of old “standbys”
  - Most not detected by “tox screens”
    - Particularly the novel drugs of abuse
  - Internet makes access easy—of course, there is no quality control
  - Doesn’t take a PhD in chemistry to “reinvent the wheel”

Resources

- Poison Center
  - 1-800-222-1222
  - Good local resource for what’s happening in your area
- www.erowid.org
  - Vaults of erowid