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)

Current Opinion in Pediatrics 2007;19:270-4
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 methylenedioxyxypyrovalerone (MDPV)
  - Methylone
  - 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.
Khat

Table 3. Outcome of Patients According to Khat Use

<table>
<thead>
<tr>
<th></th>
<th>Khat</th>
<th>No Khat</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital death, %</td>
<td>7.5</td>
<td>3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-mo Death, %</td>
<td>15.5</td>
<td>6.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-y Death, %</td>
<td>18.8</td>
<td>10.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>18.5</td>
<td>11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrent ischemia, %</td>
<td>27.7</td>
<td>12.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reinfarction, %</td>
<td>3.8</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiogenic shock, %</td>
<td>11.6</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleeding, %</td>
<td>0.8</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>1.2</td>
<td>0.6</td>
<td>0.007</td>
</tr>
<tr>
<td>Hemorrhagic, n</td>
<td>13</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Thrombotic, n</td>
<td>2</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Unknown, n</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Ventilation, %</td>
<td>6.2</td>
<td>4.2</td>
<td>0.001</td>
</tr>
<tr>
<td>VF/VT, %</td>
<td>5.6</td>
<td>2.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

VF/VT indicates ventricular fibrillation/ventricular tachycardia.

?Contributing vasospasm or hypercoagulability

Circulation, 2011
Hallucinogenic amines
Synthetic phenylethylamines

Mescaline

Peyote cactus

“BOD”

“2CI”
Hallucinogenic amines

- “2C” drugs
  - 2 carbons between amino group and benzene ring
  - Agonists at $5HT_2$ receptor
  - 2CI blocks reuptake of dopamine, serotonin, and norepi
  - Agonist at $\alpha_1$ receptor

JMT 2013
Hallucinogenic amines

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

J. Med. Toxicol.
DOI 10.1007/s13181-013-0287-x

TOXICOLOGY OBSERVATION

Recurrent Seizures and Serotonin Syndrome Following “2C-I” Ingestion

Adam Bosak • Frank LoVecchio • Michael Levine

- 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

Severe Methemoglobinemia and Hemolytic Anemia from Aniline Purchased as 2C-E (4-ethyl-2,5-dimethoxyphenethylamine), a Recreational Drug, on the Internet — Oregon, 2011
PiHKAL
Phenylethylamines I Have Known and Loved
published in 1991

Amazon price:
paperback
$20.92
PiHKAL

Detailed synthesis instructions for over 200 psychedelic compounds

13 **BOB**  4-Bromo-2,5, beta-trimethoxy-PEA
14 **BOD**  2,5, beta-Trimethoxy-4-methyl-PEA
15 **BOH**  beta-Methoxy-3,4-methylenedioxy-PEA
16 **BOHD** 2,5-Dimethoxy-beta-hydroxy-4-methyl-PEA
17 **BOM**  3,4,5, beta-Tetramethoxy-PEA
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-DIDEHYDRO-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
Synthetic cannabinoids

- 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

Figure 3. Age Distribution of Synthetic Cannabinoid and Marijuana-Related Emergency Department (ED) Visits: 2010

* Estimates for ED visits involving synthetic cannabinoids for patients aged 90 or older were suppressed due to low statistical precision.

Note: ED visits in which the patient age was unknown are excluded.

Source: 2010 SAMHSA Drug Abuse Warning Network (DAWN)

Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (December 4, 2012). The DAWN Report: Drug-Related Emergency Department Visits Involving Synthetic Cannabinoids. Rockville, MD.
Synthetic cannabinoids

- Bind variably to CB1 and CB2 receptors with higher affinity than marijuana
  - CB1 CNS – primary pharmacologic effects from cannabinoids
  - CB2 periphery
Sold as “legal cocaine”

TOXICOLOGY/CASE REPORT

MAM-2201 (Analytically Confirmed) Intoxication After “Synthacaine” Consumption

Davide Lonati, MD*; Eleonora Buscaglia, PharmD; Pietro Papa, PhD; Antonella Valli, PhD; Teresa Coccini, PhD; Andrea Giampreti, MD; Valeria Margherita Petrolini, MD; Sarah Vecchio, MD; Giovanni Serpelloni, MD; Carlo Alessandro Locatelli, MD

*Corresponding Author. E-mail davide.lonati@fsm.it.

Excitative behavior, xerostomia, chest pain, severe dyspnea, tachycardia (150 beats/min), and mild hypertension (160/80 mm Hg) without ECG abnormalities were observed in a 20-year-old subject 6 hours after nasal insufflation (snorting) of a “legally” obtained white powdered substance sold as Synthacaine. A serum sample was found to contain MAM-2201 (11 ng/mL), a synthetic cannabinoid receptor agonist, and benzocain. The patient’s symptoms improved after administration of diazepam and intravenous fluids. Synthacaine was sold as legal cocaine, suggesting the user can expect an effect like that of cocaine. The pharmacologic receptor profile and chemical structure of MAM-2201 is similar to the synthetic cannabinoid receptor agonists AM-2201 and JWH-122 (2 potent synthetic cannabinoid receptor agonists with high affinity to cannabinoid receptors). [Ann Emerg Med. 2014;64:629-632.]
Synthetic cannabinoids

- Manifestations
  - Paranoia/anxiety/psychosis
  - Hallucinations
  - Vomiting
  - Tremors/seizures
  - Tachycardia, Hypertension

- Duration: up to several hours
Synthetic cannabinoids

Myocardial Infarction Associated With Use of the Synthetic Cannabinoid K2

abstract

Designer drugs have been problematic over the years. Products such as K2 and Spice, which contain synthetic cannabinoids, are marketed as incense and are widely available on the Internet and at various specialty shops. The effects are reported as cannabis-like after smoking them. In addition, use of these synthetic cannabinoids will not appear on a routine urine toxicology screen. Recently, K2 became a popular alternative to marijuana among youths. Health implications of these designer drugs are not completely understood. Little has been reported about the harmful effects of K2. We report here the first (to our knowledge) cases of myocardial infarction (MI) after smoking K2. Three patients presented separately to the emergency department complaining of chest pain within days after the use of K2. Acute MI was diagnosed in each case on the basis of electrocardiogram changes and elevated troponin levels. Coronary angiography was performed, and the results were normal for the first 2 patients. The incidence of ST-elevation MI is low among teenagers, and association with drug use should be suspected. Public education and awareness need to be heightened about the possible health implications of K2. Pediatrics 2011;128:e1622–e1627

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KEYWORDS
myocardial infarction, marijuana, K2, coronary spasm

ABBREVIATIONS
USG—urine drug screen
HIV—human immunodeficiency virus
THC—tetrahydrocannabinol
MI—myocardial infarction
EGS—electrocardiogram

Drs Mir and Obafemi wrote the initial draft of the article, and Drs Young and Kane helped with the initial draft and revised the final draft.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-3823
doi:10.1542/peds.2010-3823

Accepted for publication Jun 28, 2011

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PEDIATRICS ISSN Numbers: Print, 0031-4005; Online, 1098-4275

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

Pediatrics 2011;128;e1622
Synthetic cannabinoids
Acute kidney injury

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

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

BRIEF COMMUNICATION

A case of acute cerebral ischemia following inhalation of a synthetic cannabinoid

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Fig. 1. Front (a) and back (b) view of the SC product package, “WTF,” that the patient brought (colour version of this figure can be found in the online version at www.informahealthcare.com/ctx).
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”

Introducing the Official...
K2 eLIQUID™
Aromatic Potpourri | Design for Electronic Vaporizing Devices
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

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

After Sodium Bicarbonate
Cocaine + Cocktails

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

CNS Neurosciences & Therapeutics

Original Article
From “Special K” to “Special M”: The Evolution of the Recreational Use of Ketamine and Methoxetamine
Ornella Corazza, Sulaf Assi & Fabrizio Schifano
School of Life and Medical Sciences, University of Hertfordshire, Hatfield, UK

2013
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
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
“Natural” Anticholinergics
Reversal with physostigmine

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
“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 = 1 Tbsp
“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
  - Oxycontin: 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
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?

Ann Emerg Med 2014;6:629632
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
Kratom

- 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