What’s Hot in the World of New and Emerging Drugs of Abuse

Objectives

• Become familiar with the new/emerging drugs of abuse
• Recognize the clinical signs and symptoms associated with these drugs
• Anticipate potential complications and caveats in the management of patients exposed to these drugs

Objectives

• Understand the limitations in interpreting laboratory data from exposure to these agents and legal implications of sale and use
Drugs of Abuse

- Drug: A substance that has a physiological effect when ingested or otherwise introduced into the body
- Recreational: Relating to or denoting drugs taken on an occasional basis for enjoyment, when socializing: "recreational drug use"

Drug Abuse

- Abuse: The improper use of something
- Addiction: Compulsive drug seeking and use despite harmful consequences

Designer Drugs

- Drugs created or marketed to avoid provisions of existing laws
- Usually analogues or derivatives of existing drugs with a modified chemical structure
- Less commonly a drug with a different chemical structure is synthesized
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History
- 1920 - 1930's
  - Opium conventions (1925) morphine was banned
  - In response Heroin and a number of alternative esters were produced
  - 1930: broad analogue provision

History
- 1960 - 1970's
  - New synthetic hallucinogens introduced (LSD, PCP)
  - San Francisco and the Haight Ashbury played a pivotal role in the psychedelic drug era

History
- 1972 - Tim Scully and Nicholas Sand were prosecuted for making the acetyl amide of LSD on the grounds that LSD had to be used to make ALD-52
- 1980's - 1990's
  - The term designer drugs was coined
  - Gained widespread popularity with the introduction of Ectasy (MDMA)
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**History**

- Numerous black market drugs marketed as Heroin, many of which were Fentanyl or Meperidine based
- One drug MPPP was found to have an impurity MPTP which caused a syndrome identical to Parkinson’s Disease – “Frozen Addicts”

**History**

- Laws were passed to give the DEA the power to emergency schedule a drug for one year, while gathering evidence to justify permanent scheduling
  - First used with MDMA
  - Used for 2C-B, AMT, BZP
- TFMPP was emergency scheduled but later reverted to legal status

**History**

- The late 1980’s and late 1990’s saw the resurgence of methamphetamine as a widespread public health concern
- 1990’s - 2004
  - Huge explosion of designer drugs being sold over the internet
  - Drugs sold as “Research Chemicals”
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History

- A “research chemical” would theoretically avoid the intent clause of the U.S. Analogue drug law
- The DEA raided multiple manufacturers and advertising via search engines (linking terms such as hallucinogenic or psychedelic) on the internet facilitated the raids

History

- Drugs were most commonly sold in powder forms
  - “not for human consumption”
- 2005 and onward
  - Broadened range of compounds sold as designer drugs
- 2015 - end of time: The sky is the limit...

Drug Users/Makers

- Seeking new highs
  - Using old drugs in new ways
  - Creating designer drugs
    - Legal
    - Less expensive
    - Less contaminated
    - More readily available
    - More desirable physiologic effect
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**New Kids on the Block**
- Spice et al...
- Bath Salts
- Molly
- Salvia
- Methoxetamine

**Curator of Services**
- John William Huffman is a professor of Organic Chemistry at Clemson University
- Beginning in 1984 Dr. Huffman and his colleagues synthesized 450 synthetic cannabinoids
- The intent was aid in the research of MS, AIDS and chemotherapy

**Curator of Services**
- In the mid 2000’s two of the synthetic cannabinoids were being sold as marijuana alternative in Germany as K2 and Spice
Spice is...well, not really nice

- "Herbal Highs"
- Available in the internet, head shops and tobacco shops
- Available since 2006 with wide availability by 2008
- AKA: Spice, Herbal Essence, K2, Lava Red, Aroma, Dream, TaiFun

Comparison of "herbal highs" composition.

Spice is...well, not really nice

- Advertised as: Room odors, Herbal Incense, Animal Feed, Plant Fertilizer, Collectibles, not for human consumption
- Said to contain natural plant products:
  - Baybean, Blue Lotus, Lion’s Tail, Indian Warrior, Dwarf, Skullcap, Pink Lotus etc.…

Comparison of "herbal highs" composition.

Spice is...well, not really nice

- Composition: Synthetic Cannabinoids
  - Higher affinity for CB1 and CB2 receptors than THC
- Lower doses cause clinical effects
  - HU-210
    - Reported to have 100X the potency THC

Comparison of "herbal highs" composition.
Spice is...well not really nice

- Titration is difficult
  - Tens to hundreds of mg/sample
  - Many preparation types
- Variations among the same product
  - No reliable similarities of type of synthetic cannabinoid


Clinical Effects

- Tachycardia
- Xerostomia
- Hypertension
- Hallucinations
- Seizures
- Psychosis
- Weakness
- Coma
- Dependence

Management

- Largely supportive, no antidotal therapy
  - Judicious use of Benzodiazepines
- UDS is negative for THC
  - Urine drug screens typically detect the 11-nor-9-carboxy-THC metabolite
- CPK among other labs, control of hyperthermia, seizure precautions
Legal Status

• In July, 2012, the US signed into Federal law a change to the Controlled Substances Act that makes Schedule I any "cannabimimetic agents"

• Cannabimimetic means any substance that is a cannabinoid receptor type 1 (CB1 receptor)

Legal Status

• The list of cannabinoid receptor agents specifically controlled include: CP-47,497; cannabicyclohexanol or CP-47,497 C8-homolog; JWH-018 and AM678; JWH-073; JWH-019; JWH-200; JWH-250; JWH-081; JWH-122; JWH-398; AM2201; AM694; SR-19 and RCS-4; SR-18 and RCS-8; JWH-203.

Bath Salts

• Generic Term
  – Collective group of agents

• Sold at tobacco shops, truck stops, mini marts, internet etc…

• Surge in use since November 2010
  – >1,100 exposures reported since January 2011

Bath salts as a "legal high".
Am J Med 2011 Nov;124(11)
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Bath Salts

- **AKA:**
  - Ivory Wave
  - Dusted
  - White Lightning
  - Hurricane Charlie
  - Scarface
  - Red Dove
  - White Dove
  - Cloud 9

Bath Salts as a "legal high". Am J Med 2011 Nov;124(11)

Bath Salts

- Cathinones
  - Constituents of the Khat plant
- Synthetic Cathinones
  - Mephedrone (4-methylcathinone)
  - MDPV (3,4-methylenedioxycathinone)
  - Methyline (3,4-methylenedioxyethylcathinone)

Pharmacology

- Structurally similar to amphetamines
  - CNS stimulant
  - Peripheral Stimulant
- Increases the release and inhibits the breakdown of neurotransmitters
  - Norepinephrine, Dopamine and Serotonin

*The toxicology of bath salts: a review of synthetic cathinones.*

Formulations and routes of administration

- Most are in powder form
  - Insufflation:
    - Effect within minutes, peaks in < 30min, rapid decline
  - Ingestion:
    - Longer duration of action
  - IV (combined with Heroin)
Clinical Effects

- Agitation
- Tachycardia
- Hypertension
- Seizures
- Palpitations
- Hallucinations, delusions
- Suicidal ideation

Prolonged Effects

The Times-Picayune
- 21 year old male used cloud 9
- Paranoid delusions for three days
- Cut his own throat and was stitched and sent home
- Died one day later from a self inflicted GSW

WNDU-Indiana
- 36 year old male
- Abused bath salts for 2 months
- Lost 50 pounds
- Had a fixed delusion that the FBI was after him
- Killed himself via CO poisoning
A Bad Case of the Munchies

Initially the viscous attack on Ronald Poppo in Miami was thought to be due to a psychosis induced by the use of bath salts.

However, upon extensive toxicological testing, only Marijuana was found in the Rudy Eugenes system.

Management

- Largely supportive, no antidotal therapy
  - Judicious use of Benzodiazepines
- CPK among other labs, control of hyperthermia, seizure precautions
- Fluid restriction until serum sodium is determined
- Not detected on a urine drug screen
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Legal Status

• The Federal drug policy of the United States reflects the fact that "bath salts" are illegal in at least forty-one states, with pending legislation in others.

• In July 2012, President Barack Obama signed a bill that amended the Federal drug policy of the United States to ban "bath salts."

Legal Status

• New York State banned the sale and distribution of the drug on May 23, 2011.

Molly

• First reported in California in the 1990's.

• Increased use since 2004.

• Piperazines as well as other chemicals.

• Sold as:
  – Pure Ecstasy
  – Bliss
  – Mash
MDMA

- 3,4-methylenedioxymethamphetamine
- methylenedioxy group addition makes it structurally similar to mescaline and conveys hallucinogenic properties

Piperazines

- Molly (1,3 Trifluoromethylphenyl piperazine) TFMPP
- Sometimes combined with Benzylpiperazine (BZP)


99 “Ecstasy” tablets
**Caveat Emptor**

- Tremendous variation in content & dose
  - 25 different types of ‘ecstasy’ pills given to investigators by users
  - Virtually none contained solely MDMA
  - Ephedrine, ketamine, acetaminophen, caffeine common adulterants


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**Other Piperazines**

- Not closely related to any familiar recreational drugs
- Synthetic, do not occur naturally
- Developed as anti-helminthic in the 1950’s
- Evaluated as an antidepressant in the 1970’s


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**MDMA**

- Indirect sympathomimetic:
  - Increases serotonin, norepinephrine, and dopamine
- Direct agonism at 5-HT₂, 5-HT₁, and D₂ receptors
- Associated with profound hyponatremia
**Pharmacology of Piperazines**

- Post synaptic serotonin agonist
- Presynaptic release of serotonin
- Inhibition of reuptake of serotonin
- No appreciable effect on norepinephrine or dopamine

**Symptoms**

- TFMPP
  - Serotonin toxicity: Nausea, HA, Anxiety, Seizures, Hyponatremia
- TFMPP + BZP
  - Agitation, anxiety, hallucinations, vomiting, insomnia


**Symptoms**

- MDMA
  - A sense of inner self
  - Diminished aggression
  - Diminished fear
  - Euphoria
  - Prosexual
  - Intensification of senses
Management

- Symptomatic supportive care
- Judicious use of benzodiazepines
- Water restriction if hyponatremic
- Consider the diagnosis of Serotonin Syndrome
- MDMA and Piperazines are not detected on a urine drug screen

Legal Status

- MDMA is Schedule I in the United States. This means it is illegal to manufacture, buy, possess, or distribute without a DEA license
- On July 18th, 2002, the DEA announced its intent to schedule BZP & TFMPP
- On September 20th the DEA issued their final order to temporarily place both BZP and TFMPP in Schedule I
- On March 18, 2004, TFMPP’s emergency scheduling was removed
- Accordingly TFMPP will no longer be controlled under the CSA after March 19, 2004
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Legal Status

• On March 18, 2004, BZP was permanently placed in Schedule I

Salvia Divinorum

• Salvia (sage) is a common perennial herb that grows throughout the world
• It is a member of the mint family
• It is not hallucinogenic
• Salvia Divinorum (Diviners Sage) is not native to any specific area, although it commonly grows in Mexico and Sierra Maztec region

Salvia Divinorum

• Salvia Divinorum contains Salvinorin-A, it is thought to be the strongest naturally occurring psychoactive compound
History of Salvinorin-A

- First described in 1982 in Mexico by Alfred Ortega
- Isolated in 1983 by Leander Julian Valdes III
- Salvinorin-B and C were also isolated
- Salvinorin-A can be synthesized by via an acetylation reaction of Salvinorin-B

Pharmacology

- Structurally distinct from other naturally occurring hallucinogens, not an alkaloid
- It acts as an agonist on the kappa opioid (high affinity)
- D2 receptor partial agonist
- No action on serotonin receptors

Salvia Divinorum

- Leaves can be chewed (lighter longer effects)
- Smoked (butane torch is recommended)
- Holding the smoke in the lungs for 20 – 40 seconds due to the slow absorption of Salvinorin-A
  - Profound and short lived, most report an unpleasant experience
Salvia Divinorum

- The peak of intensity when smoked can last anywhere from 30 seconds to 15 minutes
- The typical duration of action can be from several minutes to hours

Finally Someone Honest

- Daniel Siebert Ethnobotanist: “Salvia is not fun in the way that alcohol or cannabis can be. If you try to party with salvia, you will probably not have a good experience”

Salvia divinorum: exposures reported to a statewide poison control system over 10 years

- Retrospective review
- 37 exposures to Salvia Divinorum
- Eighteen (49%) of the exposures were to S. divinorum alone. Intentional Salvia exposures resulted in a variety of neurologic, cardiovascular, and gastrointestinal effects

Salvia divinorum: exposures reported to a statewide poison control system over 10 years

- Salvia divinorum, whether alone or in combination with alcoholic beverages and other drugs, causes neurologic, cardiovascular, and gastrointestinal effects


Management

- Symptomatic supportive care
- Judicious use of benzodiazepines for agitation
- Salvinorin-A is not detected on urine drug screens

Legal Status

- Salvia divinorum is uncontrolled in the United States by federal law, but is controlled in some states
- The federal analog act generally requires that, in order to qualify as an analog, a substance must be chemically similar to a substance which is federally scheduled
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Legal Status

- Salvinorin A is chemically unique from other scheduled substances and Salvia Divinorum, as a plant, is unlikely to be targeted by this act

Legal Status

- New Jersey:
  - Senate bill 1867 and bill 3139 which would classify Salvia Divinorum and Salvinorin-A as Schedule I controlled substances in the state, were submitted on Apr 6, 2006
  - As of May 2, 2007, neither bill has been subject to a vote

Methoxetamine

- Methoxetamine (MXE) is sold as a designer drug
- It is a derivative of Ketamine and also structurally similar to PCP
- It was created for grey market distribution
Methoxetamine

- In its pure form MXE is a white powder
- The European Monitoring Centre for Drugs and Drug Addiction first identified methoxetamine in November 2010
- By July 2011, they had identified 58 websites selling the compound

Methoxetamine

- MXE is often sold as a stand alone fish tank cleaner and can be found over-the-counter in many stores across the UK and US
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Pharmacology
- NMDA receptor antagonist
- Dopamine reuptake inhibitor

Clinical Effects
- Similar to Ketamine (desirable and undesirable)
- Self reports of undesirable effects lasting longer than that of Ketamine
- Case reports of Cerebellar toxicity have been reported

Toxicity
- Hallucinogenic effects and visual distortions similar to PCP
- Out of body or near death experience (k-hole)
- Aggressive behavior, Hypertension, muscle rigidity, blank stare, seizures
Methoxetamine associated reversible cerebellar toxicity: Three cases with analytical confirmation

- Three hospital cases of acute neurological toxicity associated with the confirmation of Methoxetamine
- Case 1: 19 year old male with severe truncal ataxia, nystagmus, incoordination and a decreased mental status. Toxicity present for 4 days with gradual recovery

- Case 2 and 3: Severe ataxia, decreased mental status and slurred speech occurring 40 minutes after nasal insufflation of MXE. Symptoms resolved in 24 hours
- MXE levels: 0.24, 0.45, 0.16mg/L respectively. There were no other drugs identified

Management

- Supportive management
- Judicious use of Benzodiazepines for agitation
- Fall precautions if ataxic or uncoordinated
- Methoxetamine is not picked up on the urine drug screen
Legal Status

- Methoxetamine is uncontrolled in the United States
- MXE is generally considered legal to buy, possess, and distribute
- If sold as a supplement, sales must conform to U.S. supplement laws
- MXE is not a controlled substance Analogue under the U.S. Analogue Act

Summary

- Designer drugs and drugs of abuse are alive and well and will continue to thrive for as long as we have mouths, noses, veins and imaginations
- There are multiple loopholes that facilitate the production and distribution of these drugs

Summary

- Analogues, as well as new compounds will continually represent a challenge to the agencies involved in the identification, legalization and prosecution of people/companies involved in making these agents