Deadly in Design: New (Novel) Psychoactive Substances Update

Disclosure

- Member of Forensic Science Network LLC, a privately held company that provides forensic services to coroners, pathologists, and the law enforcement, medical and legal communities

- The opinions expressed herein are those of the author and not those of any other individual or entity.

Objectives

At the completion of this activity, the learner should be able to:

- Recall the “classic” pills, powders, potions and paraphernalia encountered in drug seizures, emergency department presentations, and death investigations
- Describe emerging trends in the use of new (novel) psychoactive substances
- Discuss the various challenges associated with new (novel) psychoactive substances classification and identification
- Recall what is currently known about the pharmacology and toxicology of “legal highs”
- Identify common routes of controlled and new (novel) psychoactive substances administration
- Understand the limitations of clinical laboratory testing as applied to identification of new (novel) psychoactive substances
- Understand current approaches to patient treatment when new (novel) psychoactive substances use is suspected

Substance Categories Most Frequently Involved in Human Exposures (Top 25)

- Analgesics (11.29%)
- Cosmetics/Personal Care Products (7.73%)
- Cleaning Substances (Household) (7.68%)
- Sedative/Hypnotics/Antipsychotics (5.85%)
- Antidepressants (4.36%)
- Antihistamines (4.01%)
- CV Drugs (3.96%)
- Foreign Bodies/Toys/Miscellaneous (3.87%)
- Pesticides (3.22%)
- Topical Preparations (3.21%)
- Alcohols (2.66%)
- Vitamins (2.56%)
- Cough/Cold Preparations (2.38%)
- Stimulants and Street Drugs (2.32%)
- Anticonvulsants (2.20%)
- Hormones/Hormone Antagonists (2.20%)
- Antimicrobials (2.20%)
- Bites and Envenomations (2.13%)
- GI Preparations (1.88%)
- Plants (1.74%)
- Dietary Supplements/Herbals/Homeopathic (1.65%)
- Chemicals (1.51%)
- Fumes/Gases/Vapors (1.32%)
- Other/Unknown Nondrug Substances (1.24%)
- Hydrocarbons (1.24%)

Adapted from the 2014 AAPCC Annual Report

NFLIS Laboratories

25 Most Frequently Identified Drugs*

- Cannabis/THC
- Methamphetamine
- Cocaine
- Heroin
- Alprazolam
- Oxycodone
- Hydrocodone
- Buprenorphine
- Amphetamine
- Clonazepam
- Fentanyl
- Ethylene
- alpha-PVP
- XLR11
- AB-CHMINACA
- Morphine
- Diazepam
- tramadol
- Methadone
- Methadone (MDMA)
- Phencyclidine (PCP)
- Non-controlled, non-narcotic
- Hydromorphone
- Polysub/polyethylene
- AB-PINACA

* NFLIS Midyear Report 2015
European Monitoring Centre for Drugs and Drug Addiction

HTTP://WWW.EUROPEAN.HU /

PRESCRIPTION AND “CLASSIC” STREET DRUGS

Drug Overdose Rates by State

National Survey on Drug Use and Health

The Familiar

Cocaine HCl and Crack Cocaine
Clandestine Manufacture

- Houses
- Apartments
- Motel Rooms
- Storage Facilities
- Barns
- Garages
- Boats
- Backpacks
- Luggage
- Farms
- Vacant Buildings
- Vehicles
- Crawl Spaces
- Underground Bunkers

Opiates and Opioids

- **Natural**: morphine, codeine
- **Semi-synthetic**: heroin
- **Synthetics**: methadone, meperidine, oxycodone, oxymorphone, hydrocodone, hydromorphone, propoxyphene, nalbuphine, butorphanol, pentazocine, buprenorphine, fentanyl...

Papaver somniferum

From this.....
To this.. Cannabis and the Edibles Industry

Hallucinogens

Mushrooms

Psilocin/Psilocybin

Adulterants and Diluents

- Adulterant-substances added to the analyte of interest with the intent of altering its character in some way. An adulterant will typically have some pharmacologic action of its own.

- Diluent-those substances devoid of physiologic effects that are added to increase the bulk of the final product.

A Few Adulterants

- Quinine
- Diphenhydramine
- Caffeine
- Acetaminophen
- Aspirin
- Niacinamide
- Diltiazem
- Levamisole
- mCPP
- Benzocaine
- Tetracaine
- Procaine
- Cocaine
- Lidocaine
- Methamphetamine
- MDA
- Clenbuterol
- Fentanyl
- Acetyl Fentanyl.....

With A Few Diluents

- Lactose
- Sodium Bicarbonate
- Sodium Chloride
- Mannitol
- Flour
- Cornstarch
- Dextrose
- Dimethylsulfone.....
Mimic (Counterfeit) Pharmaceuticals

Produced to resemble legitimate dosage forms
Mimic tablets typically contain illicit substances

NEW (NOVEL) PSYCHOACTIVE SUBSTANCES AND TRENDS IN THEIR USE

Definition

New psychoactive substance: a new narcotic or psychotropic drug, in pure form or in preparation, that is not controlled by the 1961 United Nations Single Convention on Narcotic Drugs or the 1971 United Nations Convention on Psychotropic Substances, but which may pose a public health threat comparable to that posed by substances listed in these conventions. (Council Decision 2005/387/JHA)

More Definitions

Legal highs
- Marketed in bright/attractive packaging. Sold openly in head shops and online. Aimed at recreational users.

Research chemicals
- Sold under the pretense of being used for scientific research. Aimed at those who explore the effects of psychoactive substances. Sold openly online.

Food/Dietary Supplements
- Sold under the pretense of being food or dietary supplements. Aimed at those who desire to enhance body and mind. Sold openly in nutrition centers and online.

Designer Drugs
- Distributed as MDMA, heroin and others. Produced in clandestine labs by organized crime. Sold on the illicit drug market by drug dealers.

Medications
- Medications diverted from patients or illegally imported into Europe/US. Sold on the illicit market by drug dealers.

And The Not So Familiar

The Internet as Marketplace
In 2009, the European Monitoring Centre for Drugs and Drug Addiction Early Warning System (EWS) identified 24 new substances. In 2010, it identified 41. In 2011, there were 49 identified and in 2012, there were 73 more reported. By October 2013, an additional 56 compounds had been identified. In 2014, 101 compounds were reported.  

New Psychoactive Substances in Europe

Structural or Functional Analogs as NPS
- Production - Clandestine labs
- Lack of quality control
- Structural / functional CS analogs
- Synthesized as new “molecular entity”
- Evade regulation (CSA)
- Analytical challenges
  - Pills, Powders, Potions, Paraphernalia
  - Biological matrices
- Potent toxicological effects
- Safety and efficacy
  - Dose → Concentration → Effect
  - Emergency Department
  - Death Investigations

The Controlled Substances Analog Law
- Any new substance may be considered a controlled “analog” if:
  - It has a substantially similar structure to a Schedule I or II hallucinogen, stimulant, or opiate, AND,
  - It has the same CNS effects as the related Schedule I or II hallucinogen, stimulant, or opiate, OR,
  - It was possessed or sold with the knowledge of being an analog
- Application can be extremely difficult
- FDA Safety and Innovation Act (2012)
  - Synthetic Drug Abuse Prevention Act

Building the Case
Information Sources - Drug Use and Toxicity
- Pharmacological studies (in vitro)
- Animal studies
- Self-reports/social media/crowdsourcing
- Published case reports
- Pre-hospital emergency services data
- Emergency department presentations
- Poison Center services
- Data collection through specialist centers
Khat and the Synthetic Cathinones

Khat contains the naturally occurring alkaloid cathinone, an amphetamine-like compound with stimulant, anorexic and euphoriant properties; synthetic cathinones bear a similar structural relationship to the naturally occurring compound.
PIPERAZINES, PHENETHYLAMINES AND NBOMe SERIES

Benzylpiperazine (BZP)
- Piperazines
  - Anthelmintic (1950's)
  - Antidepressant (1970's)
  - Recreational (1990's)
- Mixed MOA
  - Serotonin
  - Dopamine
  - "Weak MDMA"
- Analogs
  - Adulterants
    - Caffeine
    - Illicit Stimulants

BZP Analogs
- 1-methyl-4-piperazine (MBZP)
- 1,4-dibenzylpiperazine (DBZP)
- 3-chlorophenylpiperazine (mCPP)
- 3-fluoromethoxybenzylpiperazine (FMBP), CI
- 3,4-methylenedioxyl-1-benzylpiperazine (MDBZP)
- 4-bromo-2,5-dimethoxy-1-benzylpiperazine (2C-B-BZP)
- 4-methoxyphenylpiperazine (MeOPP)
- Para-fluorophenylpiperazine (pFPP)

Phenethylamines
- 2C-B
- 2C-E ("Europa")
- 2C-I (precursor to NBOMe compounds)
- 2C-T-2
- 2C-T-7
- 2C-C
- 2C-P
- 2C-H
**NBOMe derivatives**

- Work by Dr. Nichols et al., discovered modifications of hallucinogenic phenethylamines increases potency

Molecular Interaction of Serotonin 5-HT_{2A} Receptor Residues Phe339 (R,S) and Phe340 (R,S) with Superpotent N-Benzyl Phenethylamine Agonists

Michael R. Braden, Jason C. Pantith, John C. Naylor, and David E. Nichols

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**Death by NBOMe**

[Image: ONE SMALL DOSE]


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**The Magic of Chemistry**

**SYNTHETIC OPIOIDS**

**MITRAGYNNINE**

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**ANALGESICS**

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**A Closer Look: Fentanyl Analogs**

- **Acetyl fentanyl**
  - 16 x potency of morphine
  - Identified alone/combo with heroin, fentanyl
  - 14 deaths: Rhode Island (2013); PA, VA, NC, SC, LA
  - Cross-reactivity with ELISA

- **Butryl fentanyl**
  - 7 x potency of morphine
  - Not scheduled; controlled substance analog
  - 5 deaths: MD (2015)
  - Cross-reactivity with ELISA

- **Becf-hydroxythiofentanyl**
  - Synthesized directly from thiofentanyl
  - 10 deaths: South Florida (early 2015)
  - No cross-reactivity with ELISA (< 50 ng/mL)

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<td>Carfentanil</td>
<td>Immobilization of large animals (veterinary practice)</td>
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**Mitragynine-Kratom**

**HALLUCINOGENS**

TRYPTAMINES
METHOXETAMINE
BHO
SYNTHETIC CANNABINOIDs
SALVIA DIVINORUM

**TRYPTAMINES**

Tryptamines

- DMT
- 5-MeO-DIPT
- 5-MeO-DPT
- 4-ACO-DMT
- 5-MeO-DMT
- 5-MeO-MIPT

- 5-MeO-AMT
- 5-MeO-DET
- 4-MeO-MIPT
- 5-MT
- AMT
- DPT

**Tryptamines**

**Tryptamines**
Methoxetamine

Butane Honey Oil (BHO)

SYNTHETIC CANNABINOIDs

Cannabinoid Research

Synthetic Cannabinoids

- John W. Huffman, Ph.D. (Clemson)
  - Research with cannabinoid receptors (CB1/CB2)
  - Hundreds of indole/pyrole derived compounds
  - Stronger agonists at CB1 receptor
- Herbal blend mixture (inert) sprayed with synthetic cannabinoids
  - Smoking products
  - "Herbal Incense"
  - Head Shops, Internet, Gas Stations
- First seen in Europe (2004)
- Manufactured outside the US
- DEA “drug of concern” (2009)
- Military Ban, Kansas (2011)
- DEA Emergency Schedule I (2011)

Cannabinoids bind reversibly to cannabinoid receptors
Cannabinoid receptor affinity dictates clinical effects
Antagonists-obesity, osteoporosis, nicotine dependence, psychiatry
Agonists-inflammation, multiple sclerosis, cancers, cardiovascular disease
Synthetic Cannabinoids

Over 100 compounds have been identified in the literature with potencies at least twice that of THC. This does not include the countless unpublished designer compounds which are likely to continue to arrive.

Reported Toxic Effects

Salvia divinorum

Administration
- Inhalation
- Chewing (“Quid”)
- Sublingual (Tincture)

Dose
- Effects
  - Onset
  - Peak
  - Duration of Action

Synthetic Cannabinoids

Salvia divinorum

“Diviner’s Sage”
Religious use (Mazatec shamans)
Salvinorin A psychoactive ingredient Potent κ-opioid/D₂ receptor agonist

CHALLENGES TO PATIENT CARE
Pick two.

Fast
Cheap
Accurate

What affects a compound’s presence in the body?
- Dose
- Dosing Interval
- Route of administration
- Distribution
- Metabolism
- Clearance
- Stability - *in vivo*

What affects the compound’s detection?
- Analyte of interest?
- “Best” Specimen
- Specimen collection/storage
- Analytical method(s)
- Stability
  - *in vivo*
  - *in vitro*
- Application of test results:
  - Clinical
  - Employee Drug Testing
  - Impaired Professionals
  - DUI/DWI
  - Death Investigation
  - Human Performance Testing....

What affects interpretation of toxicology results?
- The work of those who come before us!
- Biological matrix and specimen volume
- Analytical method(s)
- Documentation
- Knowledge/training/experience (toxicologist)
- And,
  - Case History
  - Clinical and/or Autopsy Findings
  - Postmortem redistribution
  - Criminalistics (PPPP)....

Challenges-PPPP and Toxicology
- Lack of certified reference standards
- Identification of isomers
- Increasing number of mixtures
- Difficulties in identification
  - How do we know to test for it?
  - Non-routine testing
- Limited capacity and analytical expertise (labs)
- Lack of formal PK/PD studies
- Unknown metabolites
- Selectivity and sensitivity of screening methods
- Low dose, low concentrations (biological matrices)
- Rapid metabolism of parent compound
  - Short window of analytical detection

Risk Assessment
- Physical, chemical, pharmaceutical and pharmacological information
- Potential for dependence and abuse
- Health risks
- Social risks
- Involvement of organized crime
- Prevalence level
Serious Adverse Event

Serious adverse event means any adverse event associated with consumption of a new psychoactive substance in a human that:

- results in death;
- is life-threatening;
- requires hospitalization;
- results in persistent or significant disability or incapacity;
- consists of a congenital abnormality or birth defect;
- or is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above, should also be considered dangerous.

New Psychoactive Substances in Europe-2015

We are concerned about....

- New psychoactive substances
  - New to the market
  - Newly misused
  - Changes in purity of established CS
- Nature of adulterants/diluents in established CS
  - Cocaine and Levamisole
  - Heroin and Fentanyl
- Substitutions in CS
  - Heroin sold as Cocaine
  - Fentanyl sold as Heroin
- New forms of use
  - Parenteral administration of synthetic cathinones
- Fatal/non-fatal intoxications
- Large seizures

Parting Thoughts

- Illicit drug market-evolving
- Market place: physical space to online
- Patterns of Use?
  - Acute-young, healthy, experimental attitudes
  - Chronic-adding NPS; lack of drugs of choice?
- Acute NPS toxicity-similar to “classic” drugs
  - Patient management
    - Symptomatic and supportive care
    - Duration of action appears longer
- Not all NPS are synthetics
  - If “natural” it must be safe

E-Cigarettes and Hookahs

References

- Baselt, R., Disposition of Toxic Drugs and Chemicals in Man, Biomedical Publications, Foster City, CA., 2008
- www.erowid.org
- www.scdhec.gov