Welcome to

Policies and Technologies Needed to Rein In “Designer” Drugs

May 8, 2012

#RTISPICEDRUGS
Disclosure statement

- Opinions expressed during this forum are those of the speakers and do not necessarily reflect the positions of the National Institute on Drug Abuse, Virginia Commonwealth University, RTI International or the Federal government.
Panelists

Jenny Wiley, Ph.D., RTI International
Moderator

Michael Baumann, Ph.D., National Institute on Drug Abuse
What are designer drugs?

Scott Novak, Ph.D., RTI International
Who are the users of designer drugs?

Patrick Beardsley, Ph.D., Virginia Commonwealth University
What are the current provisions for controlling the use of designer drugs?

Brian Thomas, Ph.D., RTI International
What are emerging technologies that may aid in enforcement of designer drug control provisions?
Representative Charlie Dent (R-PA)

- Sponsor of HR1254 (Synthetic Drug Control Act of 2011)
- House bill to amend Controlled Substances Act to place synthetic drugs in Schedule I
“Designer Drugs”: a formidable challenge for modern society

Michael H. Baumann, Ph.D.
Staff Scientist
Medicinal Chemistry Section
IRP, NIDA, NIH, DHHS
Baltimore, MD 21224
For the purposes of this presentation...

Designer drugs (DDs) can be defined as: legal synthetic compounds that are used as alternatives to illegal psychoactive drugs
Why do users take DDs?

- DDs are used to avoid arrest, incarceration and prosecution
- DDs are used to evade detection of drug use as assessed by urine toxicology screens
  - Military, law enforcement, athletes, etc.
- DDs are used because the illegal drug of choice is not readily available
  - Designer cathinone use may be driven by lack of Ecstasy (Brundt et al., 2010)
What are the risks of using DDs?

- The pharmacology of most DDs is not well established
  - (Carroll et al., 2012; Hill & Thomas, 2011)

- Users can not be sure of the precise chemical constituents of DD preparations
  - (Brandt et al., 2010; Brandt et al., 2011)

- Clandestine synthesis of DDs can introduce dangerous impurities or byproducts
  - (Collins et al., 2011)
The problem of DDs is not new

- **1970’s- Synthetic hallucinogens**
  - LSD analogs: LSD acetyl amide (*Orange sunshine*)
  - Phencyclidine analogs: tenocyclidine (*TCP*), psychosis

- **1980’s- Synthetic opioids**
  - Fentanyl analogs: α-methylfentanyl (*China White*), overdose
  - Meperidine analogs: MPPP, MPTP-induced Parkinsonism

- **1990’s- Synthetic stimulants**
  - Cathinone analogs: methcathinone (*Ephedrone*), Parkinsonism
  - Aminorex analogs: 4-methylaminorex (*4-Mar*), IPAH
The Internet has fostered availability and misuse of new DDs

- **Synthetic cannabinoids**
  - THC analogs: JWH-018 (*Spice*)

- **Synthetic hallucinogens**
  - Tryptamine analogs: DiPT, 5-MeO-DiPT (*Foxy*)
  - Phenylethylamine analogs: DOM, 2C-B (*Nexus*)

- **Synthetic stimulants & club drugs**
  - Piperazine analogs: mCPP, TFMPP (*Molly*), BZP (A2)
  - Methcathinone analogs: MDMC, MDPV (*Bath Salts*)
Synthetic cannabinoids (Spice, K2)
Methods of use
- Inhalation of smoke via pipes, joints, or “blunts”

Psychoactive effects
- Perceptual distortions similar to effects of marijuana
- Synthetics are much more potent than cannabis

Adverse effects
- Tachycardia, vomiting, hallucinations, panic attacks
- *(Fattore & Fratta, 2010)*
Mephedrone (4MMC, Meow, Plant food)

Methcathinone

4-Methylmethcathinone (Mephedrone)
Mephedrone

- **Methods of use**
  - Oral ingestion, snorting

- **Psychoactive effects**
  - Euphoria and empathogenic effects similar to MDMA
  - Mephedrone has a shorter duration of action than MDMA

- **Adverse effects**
  - Tachycardia, delusions, 5-HT syndrome
  - *(Prosser & Nelson, 2012)*
MDPV (*Bath salts, Ivory wave*)

Methcathinone

3,4-Methylenedioxypyrovalerone (MDPV)
Methods of use
- Oral ingestion, snorting, intravenous injection

Psychoactive effects
- Euphoria and increased energy similar to effects of stimulants
- MDPV is much more potent than cocaine

Adverse effects
- Tachycardia, agitation, hyperthermia, delirium
- (Spiller et al., 2011)
**Current list of DEA drugs of concern**

- 2C-T-7
- 2C-B
- 2C-I
- 5-MeO-DIPT
- AMT
- Anabolic Steroids
- Benzodiazepines
- BZP
- Buprenorphine
- Carisoprodol
- Clenbuterol
- Cocaine
- Cyclobenzaprine
- Dextromethorphan
- DMT
- LSD
- Fentanyl
- GHB
- Human Growth Hormone
- Hydrocodone
- Hydromorphone
- Jimson Weed
- Ketamine
- Khat
- Kratom
- Levamisol
- Mephedrone
- Methamphetamine
- Methadone
- MDMA
- MDPV
- Methylphenidate
- Nalbuphine
- Oxycodone
- Phencyclidine (PCP)
- Propofol
- Salvia Divinorum
- Spice Cannabinoids
- TFMPP
- Tramadol

[www.deadiversion.usdoj.gov/drugs_concern/index.html](http://www.deadiversion.usdoj.gov/drugs_concern/index.html)
Designer Drug Abuse: Detection and Characterization of a National Public Health Threat

Scott P. Novak, Ph.D.
Senior Research Scientist
RTI International
Dr. Novak has received contracts earned through competitive bids with the following companies:

- Eli Lilly and Company
- Shire Pharmaceuticals
- King Pharmaceuticals
- Pfizer
- Endo Pharmaceuticals
- Purdue Pharma

Funding for this presentation—NIDA (R01-030427, Novak, PI) and Substance Abuse and Mental Health Services Administration (SAMHSA)
The Available Evidence: Data Sources

- **SALVIA**
  - 16 cluster deaths in Northern Ohio in a six month period in 2011
  - 18 cluster deaths in Northern Michigan in 2011
  - Number of estimated deaths, <1,000 with 2 to 15 deaths per cluster
  - 370 Calls to poison control hotlines in 2010, in 2011 there were over 4,700

- **SYNTHETIC MARIJUANA**
  - 1,500 calls in 2010 to poison control hotlines, in 2011 about 7,000 calls
  - Several regional cluster deaths in 20 areas around the US, with 1-3 in cluster
  - Number of estimated deaths, <100
## The Available Evidence: Data Sources

<table>
<thead>
<tr>
<th></th>
<th>CEWG</th>
<th>DAWN/DEATH</th>
<th>NSDUH</th>
<th>HMO/ADMN</th>
<th>NHISBFS/MFT</th>
<th>PMPs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product specificity</strong></td>
<td>X</td>
<td>X</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Consumption</strong></td>
<td>Freq</td>
<td>None</td>
<td>Freq</td>
<td>Dose</td>
<td>Freq</td>
<td>None</td>
</tr>
<tr>
<td><strong>Motivation</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Timeliness</strong></td>
<td>X</td>
<td>✔</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Data Collection</strong></td>
<td>Client</td>
<td>Staff</td>
<td>Person</td>
<td>Tx Staff</td>
<td>Person</td>
<td>Report</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td>Med</td>
<td>Low</td>
<td>High</td>
<td>Med</td>
<td>Med</td>
<td>Low-Med</td>
</tr>
<tr>
<td><strong>Health Care Utilization</strong></td>
<td>✔</td>
<td>X</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>X</td>
</tr>
</tbody>
</table>

CEWG: Community Epi Work Group; DAWN=Drug Abuse Warning Network, NSDUH=National Survey on Drug Use and Health/MTF=Monitoring the Future, PMP=Prescription Drug Monitoring Programs
Lifetime Prevalence of Salvia: 2010 NSDUH

- Highly associated with:
  - Use of other Ecstasy (13%)
  - Illegal drug selling (18%)
  - Heroin (9%)
  - Stealing >$50 (%9)
  - Other hallucinogens (7%)
  - Marijuana (3%)
  - Major Depressive Disorder (2%)
  - Male (2% versus 1% Female)
Results from Monitoring the Future (MTF)

- Synthetic Marijuana (K2/Spice added in 2011)
- MTF is a national survey of America’s Middle and Senior High School Students (47,000 8\textsuperscript{th}, 10\textsuperscript{th}, and 12\textsuperscript{th} grade students in 400 public/private schools)
- Results: 1 in 9 reported Use of Synthetic Marijuana (11.4%)
- Limitations: School based sample
New Approaches to Public Health Surveillance

- Current substance abuse epidemiological surveys collected at fixed intervals
  - Need more intensive longitudinal data collected at shorter intervals (e.g. monthly/weekly)

- Current surveys often “miss” high risk populations (e.g., homeless/marginally housed)
  - Need rapid assessments to target high-risk areas/populations

- No consensus as to how to statistically detect an “epidemic”
  - Need indicator systems to proactively identify rapid deviations from trends to direct interventions
Data from National Survey on Drug Use and Health

- NSDUH is an annual survey of drug use and associated behaviors (55k)
- In-home sample, and marginally housed, excludes institutionalized populations (e.g., jail) and (military)

- Salvia classified as a “hallucinogen”
- Estimated 1.7 Million have tried Salvia
- Youth 18-25 have higher rates of Salvia than adults (age 26+) or (youth age 12-17)
Regulatory Control of Designer Drugs

Patrick M. Beardsley, Ph.D.

Professor, Dept. of Pharmacology & Toxicology,
Institute for Drug and Alcohol Studies,
& Center for Biomarker Research and Personalized Medicine
Virginia Commonwealth University
Regulatory Control of Drugs with Abuse Liability

- National Control
  - Federal
  - State

- International Control
Federal Regulatory Control of Drugs with Abuse Liability

- Controlled Substances Act of 1970 (CSA)
Controlled Substances Act of 1970 (CSA)

- **Purpose:**
  - combat drug trafficking
  - assure drug availability for legitimate use
  - comply with international treaties

- Established the process by which drugs are evaluated and regulated by their abuse liability

- Classification into 5 schedules (I-V) based upon abuse liability, toxicity & medical need
  - manufacture, sale, distribution, penalties
Drug Schedules

- **Schedule I**
  - high abuse liability, no medical applications, lack of accepted safety

- **Schedule II-V**
  - approved for medical use in the U.S., and vary from high (II) to limited (IV & V) psychological and/or physical dependence
Scheduling of Designer Drugs

Permanent Scheduling
- Requires many months from initiation
- In force forever unless rescheduled by re-review

Emergency Scheduling
- Requires a few months from initiation
- In force for 1 year with possible extension of 6 months
Process for Permanent Scheduling

DHHS (FDA) Conducts Medical & Scientific Review

8 Factor Analysis

Secretary of DHHS Prepares a Recommendation for Scheduling

DEA (Attorney General) Conducts Review & Decides Schedule

8 Factor Analysis

Publication of DEA Recommendation in the Federal Register

Comment Period

ALJ Hearing?

Final Order Published in Federal Register

Appeals (30 day period)?
Process for Emergency Scheduling

- Emergency scheduling authorization
- Emergency scheduling requirements
The Comprehensive Crime Control Act of 1984

- Amended section 201 of the CSA
  - gave Attorney General (DEA) the authority to temporarily place a substance into Schedule I for 1 year without regard to the requirements of 21 U.S.C. 811(b)
    - option to extend scheduling an additional 6 months
Emergency Scheduling Requirements

- **Action is necessary to avoid imminent hazard to the public safety**
- **Drug not listed in any other schedule under section 202 of the CSA (21 U.S.C. 812)**
- **No exemption or approval in effect under 21 U.S.C. 355 for the substance**
- **DEA Administrator must consider factors 4, 5 and 6 in section 201(c) of the CSA (21 U.S.C. 811(c))**
  - (4) Its history and current pattern of abuse.
  - (5) The scope, duration, and significance of abuse.
  - (6) What, if any, risk there is to the public health.
A Case History of Emergency Scheduling of 5 Synthetic Cannabinoids
Nov 1982 – Mar 2012

Nov 1982–CP-47,497 cannabimimetic activity disclosed

19 Jan 2009–University of Freiburg identifies cannabicyclohexanol as the main active ingredient in “Spice”

Nov 2008–U.S. Customs and Border Protection first detect trafficking of “Spice”
A Case History of Emergency Scheduling of 5 Synthetic Cannabinoids
Nov 1982 – Mar 2012
A Case History of Emergency Scheduling of 5 Synthetic Cannabinoids
Nov 1982 – Mar 2012

- Nov 1982–CP-47,497 cannabimimetic activity disclosed
- Nov 2008–U.S. Customs and Border Protection first detect trafficking of "Spice"
- 19 Jan 2009–University of Freiburg identifies cannabicyclohexanol as the main active ingredient in "Spice"
- Mar 2010–112 calls to U.S. poison centers
- Jan 2011–2,700 calls to U.S. poison centers

10 mos.
A Case History of Emergency Scheduling of 5 Synthetic Cannabinoids
Nov 1982 – Mar 2012

19 Jan 2009– University of Freiburg identifies cannabicyclohexanol as the main active ingredient in "Spice"

Nov 2008–U.S. Customs and Border Protection first detect trafficking of "Spice"

1 March 2011– Temporary placement of 5 synthetic cannabinoids into Schedule I

Jan 2011–2,700 calls to U.S. poison centers

24 Nov 2010–Notice of intent to schedule with justification published in Federal Register

22 Nov 2010–HHS informs DEA that there are no pending exclusions for the drugs

6 Oct 2010–DEA transmits notice to HHS of the intent to emergency schedule the drugs

Mar 2010–112 calls to U.S. poison centers

Nov 1982– CP-47,497 cannabimimetic activity disclosed

1 March 2012–DEA extends temporary placement in Schedule I by 6 months
Another Basis for Scheduling Designer Drugs

- Is the drug a “controlled substance analogue”? Relative to a Schedule I or II drug does it have:
  - Similar chemical structure?
  - ≥ Stimulant, depressant, or hallucinogenic effect?
  - Or “with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect"

Schedule I
Summary

- Sometime generous windows separate when we know a new drug has abuse potential and when it actually becomes a problem
  - Can we be proactive?

- Often small windows separate when we first see evidence of abuse until pervasive damage occurs
  - Can this window be widened?
Surveillance and Detection of Designer Drugs in the 21st Century: New Challenges in Substance Abuse and Forensic Sciences

Brian F. Thomas, Ph.D.
Senior Director - Analytical Chemistry and Pharmaceutics
RTI International
PO Box 12194
3040 Cornwallis Road
Research Triangle Park, NC 27709, USA
Tel: 9195416552
Fax: 9195416499
Email: bft@rti.org
A "10-panel urine screen" consists of the following:

- Amphetamines (including Methamphetamine)
- Barbiturates
- Benzodiazepines
- Cannabinoids (THC); Synthetic Cannabinoids (JWH-073, JWH-018, CP, …)
- Cocaine
- Methadone
- Methaqualone
- Opiates (Codeine, Morphine, Heroin, Oxycodone, Vicodin, etc.)
- Phencyclidine (PCP)
- Propoxyphene
There are currently no immunoassays screens or high-throughput broad spectrum screening approaches available for synthetic cannabinoids and other drugs of concern.

A variety of laboratories are offering to analyze herbal materials or biological fluids for the banned cannabinoids or their metabolites using targeted analytical approaches.

This approach can be problematic….and doesn’t address broad spectrum detection needs to fit the situation (it’s relatively easy to use other analogs to evade detection).
Ultra-Performance Liquid Chromatography/Quadrupole-Time-of-Flight (UPLC-qTOF) Mass Spectrometry allows extremely sensitive and simultaneous detection of a range of structurally similar compounds that may be contained in a sample.
Advanced Analytical Approach

With a single, judiciously chosen mass defect filter set at 0.05 Da, we can selectively filter for the detection of over 150 of the known JWH analogs.
With a single, judiciously chosen mass defect filter set at 0.05 Da, we can selectively filter for the detection of over 150 of the known JWH analogs. Several mass defect filters can be used simultaneously, on parent ions and fragment ions acquired using Ms°.
Prior to the DEA ban on 5 synthetic cannabinoids prevalent in synthetic cannabis, *all products (>20 different products)* purchased in the Raleigh-Durham-Chapel Hill areas of North Carolina contained at least one synthetic cannabinoid in high concentration.

- *There were no sham products*
- *All products were on shelves and actively marketed in gas stations, head shops and convenience stores*
- *There were no age limits for purchase*
- *In general, anecdotal reports of potency matched analytical results of apparent strength*
Combinations of synthetic cannabinoids were seen in several products, suggesting “tailoring” of the products for desired endpoints.
Combinations of synthetic cannabinoids were seen in several products, suggesting “tailoring” of the products for desired endpoints.

Since the DEA ban (effective March 1, 2011), new JWH-analogs and other synthetic cannabinoids have begun to be detected.
Summary of Results

Combinations of synthetic cannabinoids were seen in several products, suggesting “tailoring” of the products for desired endpoints.

Since the DEA ban (effective March 1, 2011), new JWH-analogs and other synthetic cannabinoids have begun to be detected.

Sham products are being detected, and products with pravadoline and other components have been suspected and are currently being confirmed.
Summary of Results

Combinations of synthetic cannabinoids were seen in several products, suggesting “tailoring” of the products for desired endpoints.

Since the DEA ban (effective March 1, 2011), new JWH-analogs and other synthetic cannabinoids have begun to be detected.

Sham products are being detected, and products with pravadoline and other components have been suspected and are currently being confirmed.

Analysis of ‘Bath Salts’ and other products suspected of containing mephedrone has revealed similar structural diversity being employed with these formulations.
Combinations of synthetic cannabinoids were seen in several products, suggesting "tailoring" of the products for desired endpoints.

Since the DEA ban (effective March 1, 2011), new JWH-analogs and other synthetic cannabinoids have begun to be detected.

Sham products are being detected, and products with pravadoline and other components have been suspected and are currently being confirmed.

Analysis of 'Bath Salts' and other products suspected of containing mephedrone have revealed similar structural diversity being employed with these formulations.

'Natural products' and 'dietary supplements' are also becoming increasingly common and have been found to contain a variety of active ingredients ('Lazy Cakes' with melatonin).
Conclusions

A combination of analytical approaches can be used to provide for the most effective surveillance and detection of designer drugs in a variety of formulations and biological matrices.

The AMF/MDF technique can be applied to biological fluids and metabolite identification, for confirmation of illicit use.

The information is available and searchable at www.forensicdb.org.

Effective surveillance and detection efforts will help inform the public and policy makers and deter illicit manufacture, distribution and use.

Access to authentic reference standards and research materials essential to scientific process and legal proceedings.
Thank you for attending

Patrick Beardsley, Ph.D.
Professor of Pharmacology and Toxicology
Virginia Commonwealth University
pbeardsl@vcu.edu

Scott Novak, Ph.D.
Senior Developmental Epidemiologist
RTI International
snovak@rti.org

Brian Thomas, Ph.D.
Senior Director
Analytical Chemistry and Pharmaceutics
RTI International
bft@rti.org

Jenny Wiley, Ph.D.
Senior Fellow
RTI International
jwiley@rti.org

Michael Baumann, Ph.D.
Staff Scientist
Intramural Research Program
National Institute on Drug Abuse
mbaumann@intra.nida.nih.gov

www.forensicdb.org
Searchable database for forensic information on designer drugs