SYNTHETIC DESIGNER DRUGS

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Modern Drugs Were Isolated from Plants
Certain Plants Also Yielded Pleasurable Sensations

Cathinone

\[ \begin{array}{c}
\text{C} \\
\text{H} \\
\text{O} \\
\text{N} \\
\text{H}_2 \\
\end{array} \]

\[ \text{C} \text{H}_3 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_5 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_5 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_5 \]  

\( \Delta-9\text{-tetrahydrocannabinol (THC)} \)

\[ \begin{array}{c}
\text{H}_3 \text{C} \\
\text{H}_3 \text{C} \\
\text{H}_3 \text{C} \\
\text{H}_3 \text{C} \\
\text{O} \\
\end{array} \]

\[ \text{C} \text{H}_3 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_5 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_5 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_5 \]  

Methamphetamine

\[ \begin{array}{c}
\text{C} \\
\text{H} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\end{array} \]

\[ \text{C} \text{H}_3 \]  

Heroin

\[ \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\end{array} \]

\[ \text{C} \text{H}_3 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_5 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_5 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_5 \]  

\[ \text{C} \text{H}_3 \text{C}_2 \]
Synthetic cathinones

• 3,4-DMMC
• 3-MEC
• 4-fluoroisocathinone
• 4-MEC
• 4-MePPP
• 4-methylbuphedrone
• Alpha-PBP
• alpah0PVP
• Buphedrone
• Butylone
• Dibutylone
• Dimethylone
• Ethylcathinone
• Ethylone
• Fluoromethcathinone
• Isopentedrone
• MABP
• MDPBP
• MDPPP
• MDPV
• Mephedrone
• Methedrone
• Methylone
• MOPPP
• MPHP
• Naphyrone
• N-ethylbuphedrone
• Pentedrone
• Pentylylone

51 cannabinoids
31 cathinones
76 “others” amphetamines, tryptamines, piperazines
Goals

• What are designer drugs?
• What Drives Designer Drug Markets?
• Trends?
• Are Designer Drugs legal?
• Who is using “Bath Salts” Synthetic Cannabinoids and why?
• Why are they dangerous?
• Summary
Main Categories

• Bath salts: stimulants hallucinogens, entactogens or “empathogens”
  • These are not bath salts!!!!!!! They are chemicals.

• Cannabinoids: marijuana-like
  • Synthetic marijuana-like chemicals

• Dragonflies:

• Morphine-like: Krokodil

• Tryptamines: hallucinogens
**Phenethylamines**
Related to: phenethylamine

- **2C-x**
  - Related to: mescaline
  - 2C-B 2C-D
  - 2C-I 2C-P
  - 2C-E 2C-T-x
  - 2C-B-FLY

- **Psychedelic amphetamines (DOx)**
  - Related to: 2C-x, amphetamine
  - DOB DOM
  - DOC DON
  - DOI DOET
  - Bromo-DragonFLY

- **β-ketones**
  - Related to: cathinone, MDMA, amphetamine
  - Mephedrone
  - Butylone
  - Methylylone
  - Ethylone
  - Methedrone
  - MDPV
  - Naphthylpyrrole

- **Cyclized amphetamines**
  - Related to: MDMA, amphetamine
  - 2-IAI 2-AT
  - MDAI MDAT
  - MDMAI MDMAAT
  - MAA

**Ergolines**
Related to: LSD, LSA
- PRO-LAD ETH-LAD

**Tryptamines**
Related to: psilocin, DMT, serotonin

- **5'-substituted**
  - Related to: psilocin, serotonin
  - 5-MeO-DMT 5-MeO-DALT
  - 5-MeO-MIPT 5-MeO-MET
  - 5-MeO-DIPT 5-MeO-DPT
  - 5-MeO-AMT 5-MeO-AET

- **4'-substituted**
  - Related to: psilocin
  - 4-AcO-DMT 4-HO-DPT
  - 4-AcO-DET 4-HO-DALT
  - 4-HO-MIPT 4-HO-DIPT
  - 4-MES-DMT

**Synthetic Cannabinoids**
Functionally related to naturally occurring cannabinoids
- Found in a number of branded products, most notably Spice

- CP-47,497
- CP-55,940
- JWH family
  - JWH-017 JWH-073
  - JWH-018 JWH-081
  - JWH-019 JWH-200
  - JWH-250

- CB-25 CB-52

**Piperazines**
Related to: piperazine
- BZP mCPP
- MBZP pFPP
- DBZP MeOFP
- MDBZP TFMPP

**Opiates**
a methylfentanyl
- 3-methylfentanyl
- para-fluorofentanyl
- MPPP
- O-desmethytramadol
- 7-acetoxyxymitragynine
What Are Designer Drugs?

Bath salts

Phenethylamine (PEA)

Amphetamine

Methamphetamine

MDMA or ecstasy

Cathinone

Mephedrone

Methyline

Pyrovajerone

Näphyrone

MDPV or methylenedioxyvajerone

ARE NOT
Bath salts: how to recognize

- If sold as “Bath salts”, warning signs:
  - Small packet
  - Labeled: “not for human consumption”
  - Labeled “not illegal”
  - Labeled “adults only”

- If sold as “plant food”, “fertilizer”
Plant Feed Shop offers 99.9% pure 4-MMC plant food product for botanical and laboratory research requirements. Please send email to order 4-MMC online from us. The product will be delivered in best within 2 to 4 days of ordering by air mail shipping services. At Plant Feed Shop we are the leading suppliers of plant food and research chemicals offering high quality mephedrone, bk-MDMA, MDAI, 4-MEC, MDPV, MCAT, cannabis seeds, kratom and salvia divinorum at affordable prices.
Bath Salts: stimulants, entactogens, hallucinogens

• Some based on amphetamines (ephedrone)

Some based on cathinone in plant Khat

• Often contain: methylenedioxypyrovalerone (MDPV), mephedrone, methylone
What Are Designer Drugs? Marijuana-like

THC: phyto-cannabinoid
made by plant Cannabis sativa

JWH-018: synthetic cannabinoid
made in chemistry laboratory

Anandamide: endocannabinoid
made by brain cells
What Are Designer Drugs?

**Fly**

**Phenethylamine (PEA)**

**2C-Bfly**

**Br-Dragonfly**
• Desmorphine: Russian, response to heroin supply

• Synthesis: Simple with codeine, iodine, red phosphorus.

• Purity: Highly impure, contaminated with toxic, corrosive byproducts.

• Psychoactive effects: Similar to heroin, shorter duration; brain damage

• Notoriety: Produces severe tissue damage, phlebitis, gangrene

• Life expectancies: Short
Where Did Designer Drugs Come From?

Dr. David Nichols  
Dr. John W Huffman  
Dr. Alexander Shulgin
How Was Legitimate Chemistry Transferred to “Dark Side”?

Extensive Rigid Analogue Design Maps the Binding Conformation of Potent N-Benzylphenethylamine 5-HT2A Serotonin Receptor Agonist Ligands

José U. Jiménez Jr., Martin Hanson, Lisa A. Remer, Juan Pablo Carrera, Rebecca Maguddien, John D. McGuire, Daurice Marion Lookda, Markus A. Lilje, and David E. Nicholls

Department of Medicinal Chemistry and Molecular Pharmacology, College of Pharmacy, Purdue University, West Lafayette, Indiana 47907, United States

ABSTRACT: Based on the structure of the equipotent 5-HT2A agonist 2-(4-benzyl-3,4-methylenedioxyphenyl)-1-(3-methyl-phenyl)ethanamine, which consists of a ring subst ututed phenethylamine scaffold combined with an N-benzyl group, we designed and synthesized a small library of rigid analogues with the pharamacophoric elements of the ligand. Truncated models of this ligand, in which the aromatic substitution was preserved, and new heterocycles based on the structure of (S)-5-HT2A, which shared the highest affinity of the series, we propose an optimal binding conformation. £3.5% also displayed 15-fold selectivity for the 5-HT2A receptor, indicating the most selective 5-HT2A receptor against ligand-constantly losses.

Acetylindoles: Nontubul Oncogenes and JWH-018 share in vivo cannabinoid profiles in mice

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4 Department of Chemistry and Molecular Biology, University of Virginia, Charlottesville, VA 22904-4719, USA
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1-(4-Methylphenyl)-2-pyrroolidin-1-yl-pentan-1-one (Pyrovalerone) Analogues: A Promising Class of Monoamine Uptake Inhibitors

Peter C. Meltzer,*+ David Butler,† Jeffery R. Deschamps,† and Bertha K. Madras§

Organix Inc., 240 Salem Street, Woburn, Massachusetts 01801, Naval Research Laboratory, Washington, D.C. 20375, and Department of Psychiatry, Harvard Medical School and New England Regional Primate Research Center, Southborough, Massachusetts 01772

\[ R \to 1 \to 2 \to 3 \to 4 \]

- a R = 4-CH\(_3\) (R/S)
- b R = 4-CH\(_3\) (S)
- c R = 4-CH\(_3\) (R)
- d R = H
- e R = 4-F
- f R = 4-Br
- g R = 4-I
- h R = 3-I
- i R = 4-CN
- j R = 4-CH\(_2\)OH
- k R = 4-OH
- l R = 4-CH\(_3\)COCH\(_3\)
- m R = 4-OCH\(_3\)
- n R = 4-CH\(_2\)CH\(_3\)
- o R = 4-NHCOCH\(_3\)
- p R = 4-CF\(_3\)
- q R = 4-CCCH\(_3\)
- r R = 2-CH\(_3\)
- s R = 3-CH\(_3\)
- t R = Naphthyl
- u R = 3,4-C\(_6\)
- v R = 3,4-(OH)\(_2\)
- w R = 3,4-(OCH\(_3\))\(_2\)
- x R = 4-(2-Furan)
- y R = 4-(2-Thiophene)
- z R = 4-(2-Methylpyrrole)
Marijuana distribution (CB$_1$) in Human Brain

Red, yellow regions have high concentrations of CB1 cannabinoid receptor
PET image CB1  MRI defines anatomy  MRI, PET combined

Terry et al., Quantitation of cannabinoid CB$_1$ receptors in healthy human brain using positron emission tomography and an inverse agonist radioligand. Neuroimage 48 362, 2009
Why do Medicinal Chemists Make a Variety of Compounds?

- Chemists must publish research
- How drugs dock, affect brain targets?
- Patent drugs
What Drives Designer Drugs?

- Internet: sales, production, information
- Deceptive Marketing
- “Legal” status
- Evade drug tests
- New experiences
Deceptive Marketing of Drugs
Deceive law enforcement and consumer
Marketed to teens and young adults
Retail markets and internet
Unknown composition of matter
No consistency in manufacturing
Not tested for human consumption
No information on short or long term effects
No known dosage
Likely to interact with other drugs or alcohol
National Trends: Unique Types of Synthetic Drugs Identified Nationally

NFLIS (2010-2012)

Monitor psychoactive substances ("legal highs") through Internet

- > 200 discussion forums, social media, online shops, websites, other Internet resources (YouTube, eBay, Google, Google Insight)

- > 410 substances/products (121 herbals, 153 chemicals, 140 combined)

- Information on substances with limited scientific publications

- The rise of “Spice”, mephedrone, naphyrone, MDAI and MDPV tracked from single source country, until spread

- After made illegal, online searches decrease.
Synthetic marijuana
“Bath Salts”

- 10th and 12th graders: 2nd most widely used drug after marijuana
- 3rd most widely used drug after marijuana, inhalants

Source: Monitoring the Future, Dec 2012
Adapted by CESAR from Stogner, J.M. and Miller, B.L., “A Spicy Kind of High: A Profile of Synthetic Cannabinoid Users,” *Journal of Substance Use*, Advance online publication (doi:10.3109/14659891.2013.770571), 2013. For more information, contact Dr. Stogner at stogner@email.unc.edu.
1. Actual or relative potential for abuse
2. Scientific evidence of pharmacological effects
3. State of current knowledge
4. History and current pattern of use
5. Scope, duration, significance of abuse
6. Risk to public health
   • Driving under influence, Suicides, Homicides, Drugs abused to evade drug screens, Overdose illness, deaths
7. Psychic or physiological dependence liability
8. Is substance precursor of substance already controlled
American Association of Poison Control Centers received 6,959 calls related to synthetic marijuana in 2011, *up from 2,906* in 2010.

October 2011: DEA controlled three synthetics, mephedrone, 3, 4-methylenedioxypyrovalerone (MDPV), and methylone, sold as “bath salts” “plant food”.


June 2012: 26 synthetic drugs, including 15 synthetic cannabinoids, placed under Controlled Substance Act. Actions made possession, sale of these chemicals, or products that contain them, illegal in the United States.
Are Designer Drugs Legal?

N.J. bans six chemicals used to make designer drug 'bath salts'  
Investigation: Ban on Bath Salts, Designer Drugs is Working Dramatically

STATE HEALTH OFFICER ACTS TO BAN DESIGNER DRUG (AK)  
Nebraska ban on synthetic designer drugs advances

Senator Burke (OH) working to ban designer drugs.

Florida House Committee Passes Bill to Ban 27 Substances Used in Designer Drugs

Bills banning synthetic designer drugs headed to Gov. Snyder (MI)
Calls to Poison Control Centers Decline After Drugs Scheduled (FL)

Failure of “War on Drugs”?
"Bath Salts" May Contain Designer Stimulants

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mephedrone</td>
<td>4-methyl-methcathinone; “Miaow” Similar to cocaine and MDMA (ecstasy)</td>
</tr>
<tr>
<td>Methylone</td>
<td>β-MDMA: 3,4-methylenedioxy-methcathinone; “Explosion” Similar to cocaine and MDMA (ecstasy)</td>
</tr>
<tr>
<td>MDPV</td>
<td>3,4-methylenedioxyprovalerone; MDPV; “NRG-1” (Brandt, 2010); “Ivory Wave” Stimulant with rapid onset; 2-4 hour duration of action</td>
</tr>
<tr>
<td>BZP</td>
<td>1-benzyl-piperazone Similar to amphetamine 1/10 potency of d-methamphetatmine</td>
</tr>
</tbody>
</table>

Cathinone Trends: Calls to Poison Control Centers Jan 2010 – June 2011
### Clinical Symptoms of Cathinones in Patients Admitted to ED (n=236)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>82%</td>
</tr>
<tr>
<td>Combative/Violent behavior</td>
<td>57%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>56%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>40%</td>
</tr>
<tr>
<td>Paranoia</td>
<td>36%</td>
</tr>
<tr>
<td>Confusion</td>
<td>34%</td>
</tr>
<tr>
<td>Myoclonus/Movement disorders</td>
<td>19%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>17%</td>
</tr>
<tr>
<td>CPK elevations</td>
<td>9%</td>
</tr>
</tbody>
</table>

**Source:** Spiller et al. (2011). *Clinical Toxicology*, 49, 499-505.
The “Bath Salts”: who is using, why, how?

- Energy, entactogen, hallicinogen
- Alternative to illegal stimulants; perceived as legal
- Not picked up on standard drug tests
- Available online convenience stores; head shops
- Ingestion, i.v. injection, rectal administration, insufflation as a powder, pill or capsule. Insufflation is the most common routes of administration
“Spice” and “K2”, widely used by high school and college students, are emerging public health challenges.

Their rapid rise in popularity,

- ready access from multiple sources,
- production of acute psychological distress,
- toxicity
- potentially long term harmful effects,
- ability to evade standard drug tests, require a massive public education campaign and strategies for deterrence in healthcare systems are needed to respond to this emerging threat.
Hallucinogens

1. Phenethylamines: similar to mescaline
2. Dragonfly: 2C-Bfly, Br-fly, Br-dragonfly
3. Salvinorin A: 5.9% among 12th graders
4. Tryptamines:
5. Dissociative anesthetics: methoxetamine, ketamine, PCP
6. DMAA (1,3-dimethylamylamine): “party pills”, weight loss, sports performance supplements.
## Designer Hallucinogens

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>DESCRIPTION</th>
</tr>
</thead>
</table>
| 2C-I      | Phenethylamine, via PiHKAL; stimulant and hallucinogen  
  Slow onset (1 hr); long duration of action (8-10 hr.) |
| 2C-B      | Phenethylamine, via PiHKAL; visuals  
  Faster onset (1 hr.); shorter duration than 2C-I |
| 5-MeO-DMT | Tryptamine; naturally occurring (toad, shamantic brews)  
  Smoked: almost immediate, very intense, short effect (<30 min) |
| DMT       | Tryptamine; naturally occurring  
  Smoked: almost immediate, very intense, short effect (<20 min) |

*Source: Slide courtesy of R. Bruno et al., 2011, with revisions by James Hall, 2012.*
Figure 1  2C-Phenethylamine and Tryptamine Reports to NFLIS, 2006-2010

- Tryptamines
- 2C-Phenethylamines
<table>
<thead>
<tr>
<th>2C</th>
<th>Chemical name</th>
<th>Dosage</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C-B</td>
<td>4-Bromo-2,5-dimethoxyphenethylamine</td>
<td>12–24 mg</td>
<td>4–8</td>
</tr>
<tr>
<td>2C-C</td>
<td>4-Chloro-2,5-dimethoxyphenethylamine</td>
<td>20–40 mg</td>
<td>4–8</td>
</tr>
<tr>
<td>2C-D</td>
<td>4-Methyl-2,5-dimethoxyphenethylamine</td>
<td>20–60 g</td>
<td>4–6</td>
</tr>
<tr>
<td>2C-E</td>
<td>4-Ethyl-2,5-dimethoxyphenethylamine</td>
<td>10–25 mg</td>
<td>8–12</td>
</tr>
<tr>
<td>2C-G</td>
<td>3,4-Dimethyl-2,5-dimethoxyphenethylamine</td>
<td>20–35 mg</td>
<td>18–30</td>
</tr>
<tr>
<td>2C-G-3</td>
<td>3,4-Trimethylene-2,5-dimethoxyphenethylamine</td>
<td>16–25 mg</td>
<td>12–24</td>
</tr>
<tr>
<td>2C-G-5</td>
<td>3,4-Norbornyl-2,5-dimethoxyphenethylamine</td>
<td>10–16 mg</td>
<td>32–48</td>
</tr>
<tr>
<td>2C-I</td>
<td>4-Iodo-2,5-dimethoxyphenethylamine</td>
<td>14–22 mg</td>
<td>6–10</td>
</tr>
<tr>
<td>2C-N</td>
<td>4-Nitro-2,5-dimethoxyphenethylamine</td>
<td>100–150 mg</td>
<td>4–6</td>
</tr>
<tr>
<td>2C-P</td>
<td>4-Propyl-2,5-dimethoxyphenethylamine</td>
<td>6–10 mg</td>
<td>10–16</td>
</tr>
<tr>
<td>2C-SE</td>
<td>4-Methylseleno-2,5-dimethoxyphenethylamine</td>
<td>~100 mg</td>
<td>6–8</td>
</tr>
<tr>
<td>2C-T</td>
<td>4-Methylthio-2,5-dimethoxyphenethylamine</td>
<td>60–100 mg</td>
<td>3–5</td>
</tr>
<tr>
<td>2C-T-2</td>
<td>4-Ethylthio-2,5-dimethoxyphenethylamine</td>
<td>12–25 mg</td>
<td>6–8</td>
</tr>
<tr>
<td>2C-T-4</td>
<td>4-Isopropylthio-2,5-dimethoxyphenethylamine</td>
<td>8–20 mg</td>
<td>12–18</td>
</tr>
<tr>
<td>2C-T-7</td>
<td>4-Propylthio-2,5-dimethoxyphenethylamine</td>
<td>10–30 mg</td>
<td>8–15</td>
</tr>
<tr>
<td>2C-T-8</td>
<td>4-Cyclopropylthio-2,5-dimethoxyphenethylamine</td>
<td>30–50 mg</td>
<td>10–15</td>
</tr>
<tr>
<td>2C-T-9</td>
<td>4-(t)-Butylthio-2,5-dimethoxyphenethylamine</td>
<td>60–100 mg</td>
<td>12–18</td>
</tr>
<tr>
<td>2C-T-13</td>
<td>4-(2-Methoxyethylthio)-2,5-dimethoxyphenethylamine</td>
<td>25–40 mg</td>
<td>6–8</td>
</tr>
<tr>
<td>2C-T-15</td>
<td>4-Cyclopropylthio-2,5-dimethoxyphenethylamine</td>
<td>&gt;30 mg</td>
<td>Several hours</td>
</tr>
<tr>
<td>2C-T-17</td>
<td>4-(s)-Butylthio-2,5-dimethoxyphenethylamine</td>
<td>60–100 mg</td>
<td>10–15</td>
</tr>
<tr>
<td>2C-T-21</td>
<td>4-(2-Fluoroethylthio)-2,5-dimethoxyphenethylamine</td>
<td>8–12 mg</td>
<td>7–10</td>
</tr>
</tbody>
</table>
**Dragonfly Deaths**

- Ring-substituted phenethylamines, commonly known as 2Cs, are designer drugs that are emerging as new drugs of abuse.
- The published literature concerning 2Cs is limited.
- A few 2Cs have been studied, i.e., 2C-T-7, 2C-B, and 2C-E, with limited information.
- A syndrome consistent with excited delirium including severe agitation, aggression, violence, seizures, and hyperthermia is consistently depicted in lethal 2C cases.
- There are currently no antidotes for 2C intoxication.
- Treatment is limited to supportive care but should include rapid sedation and aggressive treatment of severe hyperthermia in 2C cases presenting with signs and symptoms consistent with a syndrome of excited delirium.
## Methoxamine and methylhexanamine

<table>
<thead>
<tr>
<th>Methoxamine</th>
<th>Methylhexanamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2011</td>
<td>• Stimulant</td>
</tr>
<tr>
<td>• Dissociative, pain suppression</td>
<td>• Dietary supplement market</td>
</tr>
<tr>
<td>• Sold as ketamine derivative</td>
<td>• Cathinone replacement</td>
</tr>
<tr>
<td>• Similar to PCP</td>
<td>• Deaths</td>
</tr>
<tr>
<td>• 5-7 hour duration</td>
<td>• DMAA FDA challenges for safety evidence</td>
</tr>
<tr>
<td>• Deaths</td>
<td></td>
</tr>
</tbody>
</table>
Methoxetamine and 3,4-methoxy analogues of PCP are NMDA receptors

What Concerned People Can Counsel

• Avoid consuming drugs that affect thinking, feelings, judgment.
• The adolescent brain is fragile as it is not fully formed.
• No one knows what a street drug contains, how much, impurities, toxins.
• Intoxication is risky, for health, for making unsafe or unhealthy choices.
• Any drug, legal or not, if not prescribed / used for medical purposes, can be unsafe.
• No one knows long term effects of designer drugs.
Faustian Bargains
Drug Use and Drug Policy
Death Rates 3-5 Times Higher in Addicted Patients

Standardized Mortality Rates of Patients with a Primary Substance Use Disorder (SUD)

1 = no added risk

This is a defense of our brains!
“Bath Salts” Affect Many Organs

- Brain
- Eyes, ears, nose, throat
- Lungs
- Heart, blood vessels
- Kidney, hormones
- Digestive tract
- Reproduction
- Developing fetus

• Palpitations, shortness of breathe, chest pain, dry mouth, abdominal pain, anorexia, vomiting, erectile dysfunction, discoloration of the skin, muscular tension.
“Bath Salts”: Psychoactive Effects?

• Aggression, dizziness, memory loss, seizures, blurred vision, anxiety, hallucinations, depression, dysphoria, euphoria, fatigue, increased energy and decreased concentration, panic and paranoia.

• In several surveys of mephedrone users, 50% considered it to be addictive, nearly half reported continuous use for more than 48 hours, and more than 30% reported fulfilling three or more criteria for abuse/addiction, according to DSM-IV.

• A different survey (n=1,006) found that 17.5% of users reported symptoms of addiction, with the highest frequency of daily use falling in the 11-15 year old age range.
# Medical Effects of Cathinones

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Palpitations, tachycardia, chest pain, vasoconstriction, myocardial infarct.</td>
</tr>
<tr>
<td>Psychological</td>
<td>Aggression, anger, anxiety, agitation, auditory visual hallucinations, depression, dysphoria, empathy, euphoria, fatigue</td>
</tr>
<tr>
<td>Neurological</td>
<td>Seizures, tremor, dizziness, memory loss, cerebral edema, headaches, lightheaded</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthralgia, coldness, numbness, discoloration, numbness, tingling of limbs, muscular tension, cramping</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain, anorexia, nausea, vomiting</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Shortness of breathe</td>
</tr>
<tr>
<td>Ears, nose, throat</td>
<td>Dry mouth, nasal pain, tinnitus</td>
</tr>
</tbody>
</table>
Biology of “Bath Salts”
3,4-Methylenedioxyxypyrovalerone (MDPV)
Not all cathinones confer the same effects or health risks.

Nonetheless, they engender unacceptable risks and adverse consequences:

- (a) emergency department mentions,
- (b) persistence of effects after 24 hours,
- (c) addictive potential,
- (d) psychiatric and cardiovascular effects,
- (e) deaths.
Synthetic Cannabinoids (Marijuana) 
K2; Spice
Calls to Poison Control Center for Synthetic Cannabinoids Jan 2010-June 2011

National Counts of Exposure Calls: Synthetic Cannabinoids

| Month | Jan '10 | Feb '10 | Mar '10 | Apr '10 | May '10 | Jun '10 | Jul '10 | Aug '10 | Sep '10 | Oct '10 | Nov '10 | Dec '10 | Jan '11 | Feb '11 | Mar '11 | Apr '11 | May '11 | Jun '11 |
|-------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Calls | 24      | 33      | 99      | 116     | 201     | 176     | 249     | 326     | 345     | 418     | 489     | 471     | 408     | 451     | 547     | 571     | 617     | 643     |
K2, Spice overview

- Synthetic forms of marijuana.
- Mixture of dried, shredded plants sprayed with THC-like chemicals; THC is the most active constituent of marijuana.
- Strong clove smell
- Onset time: 5-15 minutes (smoked)
- Duration: 1-8 + hours
- Synthetic marijuana effects can be extreme of smoked marijuana or different.
- Hallucinogenic
# Psychoactive Effects

## Positive Psychoactive Effects
- Pleasant
- Euphoria
- Relaxation
- Sedation

## Negative Psychoactive Effects
- Severe paranoia, endangering self, others
- Agitation, delirium
- Headaches
- Anxiety, panic attacks
- Loss of control
- Confusion, hallucinations, psychosis
- Suicidal thoughts
- Seizures, tremors
- Impaired short-term memory concentration
- Persistent psychosis
“K2, Spice” Affect Many Organs

- Brain
- Eyes, ears, nose, throat
- Lungs
- Heart, blood vessels
- Kidney, hormones
- Digestive tract
- Reproduction
- Developing fetus

- Vomiting, nausea
- Eye soreness
- Profuse sweating
- Severe GI symptoms
- Muscle spasms
- Increased blood pressure, heart rate
- Chest Pain
- Serious injury or death
## Comparison of Marijuana and Synthetic Cannabinoids

<table>
<thead>
<tr>
<th>Cannabis ~ Cannabinoids</th>
<th>Symptoms More Typical of Synthetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>Seizures</td>
</tr>
<tr>
<td>Reddened eyes</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Anxiousness</td>
<td>High blood pressure</td>
</tr>
<tr>
<td>Mild sedation</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Agitation</td>
</tr>
<tr>
<td>Acute psychosis</td>
<td>Violent behavior</td>
</tr>
<tr>
<td>Memory deficits</td>
<td>Coma</td>
</tr>
</tbody>
</table>

Abusers in ER seek treatment for addiction
Multiple deaths associated with these alone or combined

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological</td>
<td>Anxiety, aggression, agitation, confusions, dysphoria, paranoia, irritation, panic attack, hallucinations</td>
</tr>
<tr>
<td>Neurological</td>
<td>Seizures, loss of consciousness</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, hypertension, chest pain, cardiac ischemia</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hypokalemia, hyperglycemia</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Autonomic, other</td>
<td>Fever, mydriasis conjunctivitis,</td>
</tr>
</tbody>
</table>
Acute Kidney Injury Associated with Synthetic Cannabinoid Use

CDC: Multiple States, 2012 MMWR Weekly February 15, 2013 / 62(06);93-98
Smiles or 25-I

- “Smiles” or "25-I“: analog of 2C-B, 1 drug is the newest of "research chemicals" available for purchase online.
- Psychoactive effects: hallucinations, in some cases severe brain hemorrhaging, death.
- Trend in use in Connecticut: among high school and college students.
- Unaware of potentially fatal side effects.
- 25-I's chemical makeup varies from batch to batch, approximates the effects of LSD, 2C-I, and 2C-B, all banned under federal law.
Marijuana plant makes
~ 80 phytocannabinoids
THC =#1

Brain, other organs make Endocannabinoids
Anandamide: arachidonoylethanolamide
2-AG: 2-arachidonoylglycerol
7 or more made in brain and in other tissues

Synthetic cannabinoids: 1,000s made by chemists
\( \Delta 9\text{-THC} \) (Gaoni & Mechoulam, 1964)
Δ9-THC, others, endocannabinoids target similar cannabinoid receptors

Endocannabinoid
made by the brain

Anandamide

Drug
THC made by the plant, Cannabis Sativa
Brain Cannabinoid System Controls Communication

- Modulates brain communication by reducing chemical messages
- Critical for brain development
- Controls chemical messages critical for pleasure, mood, pain, appetite, motivation, memory

• THC affects anandamide control of brain signals
• THC effects are prolonged, more powerful, different
Long Term Effects

- Addiction to JWH-018, JWH-200, JWH-073, CP-47,497, cannabicyclohexanol: physiological and psychological dependence *liability* similar to that of marijuana and THC.

- Physical and psychological withdrawal: elevated blood pressure, restlessness, drug craving, nightmares, sweating, nausea, tremor and headache, palpitation, insomnia, headache, diarrhea, vomiting.
“Spice” and “K2”, widely used by high school and college students, are emerging public health challenges.

Their rapid rise in popularity,

• ready access from multiple sources,
• production of acute psychological distress,
• toxicity
• potentially long term harmful effects,
• ability to evade standard drug tests, require a massive public education campaign and strategies for deterrence in healthcare systems are needed to respond to this emerging threat.
Hallucinogens

1. Phenethylamines: similar to mescaline
2. Dragonfly: 2C-Bfly, Br-fly, Br-dragonfly)
3. Salvinorin A: 5.9% among 12th graders
4. Tryptamines:
5. Dissociative anesthetics: methoxetamine, ketamine, PCP
6. DMAA (1,3-dimethylamylamine): “party pills”, weight loss, sports performance supplements.
## Designer Hallucinogens

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>DESCRIPTION</th>
</tr>
</thead>
</table>
| 2C-I        | Phenethylamine, via PiHKAL; stimulant and hallucinogen  
                          Slow onset (1 hr); long duration of action (8-10 hr.)                                      |
| 2C-B        | Phenethylamine, via PiHKAL; visuals  
                          Faster onset (1 hr.); shorter duration than 2C-I                                         |
| 5-MeO-DMT   | Tryptamine; naturally occurring (toad, shamantic brews)  
                          Smoked: almost immediate, very intense, short effect (<30 min)                        |
| DMT         | Tryptamine; naturally occurring  
                          Smoked: almost immediate, very intense, short effect (<20 min)                          |

Dragonfly

Figure 1  2C-Phenethylamine and Tryptamine Reports to NFLIS, 2006-2010

- Tryptamines
- 2C-Phenethylamines

Number of Reports

2006  2007  2008  2009  2010

0  100  200  300  400  500

3-bromo-2,5-dimethoxyphenethylamine (2C-B)
<table>
<thead>
<tr>
<th>Code</th>
<th>Chemical Name</th>
<th>Dosage</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C-B</td>
<td>4-Bromo-2,5-dimethoxyphenethylamine</td>
<td>12–24 mg</td>
<td>4–8</td>
</tr>
<tr>
<td>2C-C</td>
<td>4-Chloro-2,5-dimethoxyphenethylamine</td>
<td>20–40 mg</td>
<td>4–8</td>
</tr>
<tr>
<td>2C-D</td>
<td>4-Methyl-2,5-dimethoxyphenethylamine</td>
<td>20–60 g</td>
<td>4–6</td>
</tr>
<tr>
<td>2C-E</td>
<td>4-Ethyl-2,5-dimethoxyphenethylamine</td>
<td>10–25 mg</td>
<td>8–12</td>
</tr>
<tr>
<td>2C-G</td>
<td>3,4-Dimethyl-2,5-dimethoxyphenethylamine</td>
<td>20–35 mg</td>
<td>18–30</td>
</tr>
<tr>
<td>2C-G-3</td>
<td>3,4-Trimethylene-2,5-dimethoxyphenethylamine</td>
<td>16–25 mg</td>
<td>12–24</td>
</tr>
<tr>
<td>2C-G-5</td>
<td>3,4-Norbornyl-2,5-dimethoxyphenethylamine</td>
<td>10–16 mg</td>
<td>32–48</td>
</tr>
<tr>
<td>2C-H</td>
<td>4-Iodo-2,5-dimethoxyphenethylamine</td>
<td>14–22 mg</td>
<td>6–10</td>
</tr>
<tr>
<td>2C-J</td>
<td>4-Nitro-2,5-dimethoxyphenethylamine</td>
<td>100–150 mg</td>
<td>4–6</td>
</tr>
<tr>
<td>2C-K</td>
<td>4-Propyl-2,5-dimethoxyphenethylamine</td>
<td>6–10 mg</td>
<td>10–16</td>
</tr>
<tr>
<td>2C-Q</td>
<td>4-Methylseleno-2,5-dimethoxyphenethylamine</td>
<td>~100 mg</td>
<td>6–8</td>
</tr>
<tr>
<td>2C-S</td>
<td>4-Methylthio-2,5-dimethoxyphenethylamine</td>
<td>60–100 mg</td>
<td>3–5</td>
</tr>
<tr>
<td>2C-T</td>
<td>4-Ethylthio-2,5-dimethoxyphenethylamine</td>
<td>12–25 mg</td>
<td>6–8</td>
</tr>
<tr>
<td>2C-T-2</td>
<td>4-Isopropylthio-2,5-dimethoxyphenethylamine</td>
<td>8–20 mg</td>
<td>12–18</td>
</tr>
<tr>
<td>2C-T-4</td>
<td>4-Cyclopropylthio-2,5-dimethoxyphenethylamine</td>
<td>10–30 mg</td>
<td>8–15</td>
</tr>
<tr>
<td>2C-T-7</td>
<td>4-Propylthio-2,5-dimethoxyphenethylamine</td>
<td>30–50 mg</td>
<td>10–15</td>
</tr>
<tr>
<td>2C-T-8</td>
<td>4-Cyclopropylmethylenethio-2,5-dimethoxyphenethylamine</td>
<td>30–50 mg</td>
<td>10–15</td>
</tr>
<tr>
<td>2C-T-9</td>
<td>4-(t)-Butylthio-2,5-dimethoxyphenethylamine</td>
<td>60–100 mg</td>
<td>12–18</td>
</tr>
<tr>
<td>2C-T-13</td>
<td>4-(2-Methoxyethylthio)-2,5-dimethoxyphenethylamine</td>
<td>25–40 mg</td>
<td>6–8</td>
</tr>
<tr>
<td>2C-T-15</td>
<td>4-Cyclopropylthio-2,5-dimethoxyphenethylamine</td>
<td>&gt;30 mg</td>
<td>Several hours</td>
</tr>
<tr>
<td>2C-T-17</td>
<td>4-(s)-Butylthio-2,5-dimethoxyphenethylamine</td>
<td>60–100 mg</td>
<td>10–15</td>
</tr>
<tr>
<td>2C-T-21</td>
<td>4-(2-Fluoroethylthio)-2,5-dimethoxyphenethylamine</td>
<td>8–12 mg</td>
<td>7–10</td>
</tr>
</tbody>
</table>
• Ring-substituted phenethylamines, commonly known as 2Cs, are designer drugs that are emerging as new drugs of abuse.

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Agent</th>
<th>Route</th>
<th>Dose</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-year-old male</td>
<td>2C-T-7</td>
<td>Snorted</td>
<td>35 mg</td>
<td>Vomiting, hallucinations, agitation, violence/aggression, nasal bleeder, possible seizure activity, pulmonary edema, cardiac, pulmonary arrest</td>
</tr>
<tr>
<td>17-year-old male</td>
<td>2C-T-7</td>
<td>Snorted</td>
<td>Unknown</td>
<td>Agitation, violence, aggression, possible hyperthermia (removal of clothing), rigidity, cardio-pulmonary arrest</td>
</tr>
<tr>
<td>Unknown, 20-year-old male</td>
<td>2C-T-7, 200 mg MDMA</td>
<td>Unknown (dipped in water for 2 min)</td>
<td>Hyperthermia (108 °C), seizures, coma</td>
<td></td>
</tr>
<tr>
<td>22-year-old male</td>
<td>2C-T-21</td>
<td>Ingestion</td>
<td>Unknown</td>
<td>Aggressive/agitation, hyperthermia, DIC, multi-organ failure</td>
</tr>
<tr>
<td>19-year-old male</td>
<td>2C-E</td>
<td>Snorted</td>
<td>Unknown</td>
<td>Hyperthermia, swelling, red mouth</td>
</tr>
<tr>
<td>17-year-old male</td>
<td>2C-I-NBOMe</td>
<td>Ingestion</td>
<td>Unknown</td>
<td>Hyperthermia, swelling, red mouth</td>
</tr>
<tr>
<td>18-year-old male</td>
<td>2C-I-NBOMe</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Hyperthermia, swelling, red mouth</td>
</tr>
</tbody>
</table>

• The published literature concerning 2Cs is limited.

• A few 2Cs have been studied, i.e., 2C-T-7, 2C-B, and 2C-E, with limited information.

• A syndrome consistent with excited delirium including severe agitation, aggression, violence, seizures, and hyperthermia is consistently depicted in lethal 2C cases.

• There are currently no antidotes for 2C intoxication.

• Treatment is limited to supportive care but should include rapid sedation and aggressive treatment of severe hyperthermia in 2C cases presenting with signs and symptoms consistent with a syndrome of excited delirium.
## Methoxamine and Methylhexanamine

<table>
<thead>
<tr>
<th>Methoxamine</th>
<th>Methylhexanamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2011</strong></td>
<td><strong>Stimulant</strong></td>
</tr>
<tr>
<td>Dissociative, pain suppression</td>
<td>Dietary supplement market</td>
</tr>
<tr>
<td>Sold as ketamine derivative</td>
<td>Cathinone replacement</td>
</tr>
<tr>
<td>Similar to PCP</td>
<td>Deaths</td>
</tr>
<tr>
<td>5-7 hour duration</td>
<td>DMAA FDA challenges for safety evidence</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
</tr>
</tbody>
</table>
Methoxetamine and 3,4-methoxy analogues of PCP are NMDA receptors

What Concerned People Can Counsel

• Avoid consuming drugs that affect thinking, feelings, judgment.
• The adolescent brain is fragile as it is not fully formed.
• No one knows what a street drug contains, how much, impurities, toxins.
• Intoxication is risky, for health, for making unsafe or unhealthy choices.
• Any drug, legal or not, if not prescribed / used for medical purposes, can be unsafe.
• No one knows long term effects of designer drugs.
Faustian Bargains
Drug Use and Drug Policy
Death Rates 3-5 Times Higher in Addicted Patients

Standardized Mortality Rates of Patients with a Primary Substance Use Disorder (SUD)

1 = no added risk

This is a defense of our brains!