Chemistry & Drug Metabolism Research Program

- Utilize pharmacological & toxicological tools to
  - Address mechanisms underlying human drug abuse & addiction
  - Investigate behavioral & physiological drug toxicities
  - Develop new prevention strategies & treatment medications

- Conduct controlled drug administration studies in humans to determine onset, peak & duration of drug effects & time course of markers in biological matrices
Chemistry & Drug Metabolism Research Program

- Data provide a framework for understanding mechanisms of drug action & toxicity, & for predicting drug effects in individual patients

- Research directly impacts public health & safety
  - Data for evidence-based drug policy & legislation
  - Identify new metabolic pathways & metabolites (designer drugs)
  - Improve monitoring tools to deter & identify drug use
  - Document medication efficacy when assessing new pharmacological or behavioral drug treatments
  - Create new tools for drug abuse practitioners
National Institute on Drug Abuse IRP
Designer Drug Initiative

SURVEILLANCE
Terry Boos, PhD, DEA
Moira O’Brien, PhD, CEWG

PRECLINICAL PHARMACOLOGY
Mike Baumann, PhD, NIDA IRP

TOXICOLOGY
ASSESSMENTS
Aidan Hampson, PhD, NIDA HQ

CLINICAL INVESTIGATIONS
Marilyn Huestis, PhD, NIDA IRP

DATA DISSEMINATION
Presentations, Publications, Internet
National Institute on Drug Abuse Intramural Research Program Designer Drug Initiative

• Characterize pharmacokinetics of designer drugs in humans
  • Cultured hepatocyte incubation with designer drugs
  • Human liver microsome incubation with designer drugs
  • High resolution mass spectrometric analysis of phase 1 & 2 metabolites
  • High resolution time of flight designer drug screen
Pharmacology of Designer Drugs

- Drug
  - Absorption
  - Binding and Storage in Tissue
    - Protein
    - Fat
  - Biliary Excretion
    - Enterohepatic Circulation
  - Renal Excretion
    - Glomerular Filtration
    - Tubular Secretion
    - Passive Reabsorption

- Blood Concentrations
  - Binding to Serum Proteins
    - Albumins
    - Lipoproteins
  - Placenta
  - Biotransformation
    - Hepatic Microsomes
    - Non-Microsomal
    - Extrahepatic
  - Metabolites
    - Inactive
    - Active
  - Hair/Oral Fluid/Sweat/Breast Milk
  - Biliary Excretion
    - Enterohepatic Circulation
  - Renal Excretion
    - Glomerular Filtration
    - Tubular Secretion
    - Passive Reabsorption
  - Drug Concentration
  - Site of Action
  - Competition & Neuroadaptation
  - Drug Concentration
  - Site of Action
  - Receptor Occupancy
  - Intensity of Effect

- Adverse Effects
  - Additive or Reductive Effects
    - Other Drugs
    - Physiological Interactions
    - Disease State
    - Age

- Drug Concentration
- Site of Action
- Receptor Occupancy
- Intensity of Effect
Designer Drug Problem Isn’t New

- 1970’s- Synthetic hallucinogens
  - LSD analogs: LSD acetyl amide (*Orange sunshine*)
  - Phencyclidine analogs: tenocyclidine (*TCP*)
- 1980’s- Synthetic opioids
  - Fentanyl analogs: α-methylfentanyl
  - Meperidine analogs: MPPP, MPTP-induced Parkinsonism
- 1990’s- Synthetic stimulants
  - Cathinones: methcathinone
  - Aminorex: 4-methylaminorex
NFLIS 2011
Hallucinogen Reports

N = 45,382

MDMA 20.5%
Psilocybin 13.5%
AM-2201 10.7%
JWH-018 6.6%
5-MeO-DiPT 5.5%
JWH-250 5.2%
JWH-122 4.8%
TFMPP 3.7%
Methylone 3.3%
JWH-081 2.3%
JWH-073 1.1%
RCS-4 1.2%
Other Hallucinogens 9.3%

N = 45,382
Synthetic Cannabinoids
JWH, AM, HU, XLR, UR

K2 Spice Zohai
Bombay Blue Black
Mamba Genie Skunk
Moon Rocks Blaze
Yucatan Fire Genie
Synthetic Cannabinoids Pharmacology

- Primarily smoked, delivers drug rapidly to brain
- High abuse liability
- Agonists at CB1 &/or CB2 receptors with wide variability in binding affinity
- Binding evaluated in rodent brain, Chinese hamster ovarian cells, human embryonic kidney cells, human receptor preparations
- Most more potent than Δ9-tetrahydrocannabinol (THC)
Cannabinoid Receptors

**CB₁**
- Central nervous system
- Cardiovascular system
- Reproductive system

**CB₂**
- Immune system
- Spleen, Tonsils & Lymphoid tissues

Non-CB1, Non-CB2 Receptors
## SC Receptor Binding Affinity compared to THC ($\text{CB}_1 \ K_i = 5 - 80 \ \text{nM}$)

<table>
<thead>
<tr>
<th>Drug</th>
<th>$\text{CB}_1 \ K_i$ (nM)</th>
<th>$\text{CB}_2 \ K_i$ (nM)</th>
<th>THC $\text{CB}_1 \ K_i / \text{SC} \ \text{CB}_1 \ K_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM694</td>
<td>0.1</td>
<td>1.4</td>
<td>50 - 805</td>
</tr>
<tr>
<td>AM2201</td>
<td>1.0</td>
<td>2.6</td>
<td>5 - 80</td>
</tr>
<tr>
<td>HU210</td>
<td>0.1</td>
<td>0.5</td>
<td>50 - 800</td>
</tr>
<tr>
<td>JWH018</td>
<td>9.0 ± 5.0</td>
<td>2.9 ± 2.7</td>
<td>0.5 – 9.0</td>
</tr>
<tr>
<td>JWH073</td>
<td>8.9 ± 1.8</td>
<td>38.0 ± 24.0</td>
<td>0.6 – 9.0</td>
</tr>
<tr>
<td>JWH081</td>
<td>1.2 ± 0.03</td>
<td>12.4 ± 2.2</td>
<td>4.2 – 67.1</td>
</tr>
<tr>
<td>JWH250</td>
<td>11.0 ± 2.0</td>
<td>33.0 ± 2.0</td>
<td>0.5 – 7.3</td>
</tr>
<tr>
<td>UR144</td>
<td>150</td>
<td>1.8</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>
High CB1 Receptor Density

Brain Stem & Spinal Cord
- Vomiting reflex & Pain sensation

Amygdala
- Anxiety, Emotion & Fear

Basal Ganglia
- Motor control & planning

Hypothalamus
- Appetite, Hormones & Sexual behavior

Hippocampus
- Memory & Learning

Neocortex
- High cognitive function & Sensory data integration

Cerebellum
- Motor control & coordination

Hypothalamus
- Appetite, Hormones & Sexual behavior

Neocortex
- High cognitive function & Sensory data integration
Endogenous Cannabinoids

- Different routes of synthesis
- Different modes of degradation (FAAH & MAGL)
- Different efficacy

Anandamide (AEA)

2-Arachidonoyl glycerol (2AG)
Endocannabinoid Signaling

Presynaptic neuron

Postsynaptic CB₁ receptor

Presynaptic CB₁ receptor stimulation inhibits release of classical neurotransmitters

Postsynaptic receptor

Endocannabinoids

Presynaptic neuron
Synthetic Cannabinoids Pharmacology

- Limited pharmacodynamic research on rodents & non-human primates
- Few human data
  - 1 limited controlled administration study
  - Multiple self-administered single dose studies
  - Emergency room & police reports
  - Internet posts
### Preclinical Acute vs Chronic Exposure (14 day)

**Acute**
- Analgesia
- Anti-emetic
- Anti-epileptic
- Anxiolytic (low dose)/Anxiogenic (high dose)
- Decrease locomotion/catalepsy (high dose)
- Hypothermia/Hypotension
- May produce relapse in formerly drug-dependent animals

**Chronic**
- Cognitive impairment
- Anti-inflammatory
- Immunosuppressant
- Anxiogenic
- Facilitated sensitization to other drugs
Acute vs Chronic Human Exposure

- **Acute**
  - Agitation & anxiety
  - Chest pain & tachycardia
  - Hypertension
  - Muscle twitches
  - Nausea & vomiting
  - Short-term memory & cognitive impairment
  - Shortness of breath
  - Paranoia/Hallucinations
  - Reddened conjunctivae & dilated pupils

- **Chronic**
  - Psychosis/Paranoia
  - Withdrawal
    - Increased craving
    - Hypertension
    - Muscle twitches
    - Restlessness
    - Sweating
    - Tachycardia
[^18F]FMPEP-d$_2$ Labels CB1 Cannabinoid Receptors in Brain of Chronic Daily Cannabis Smokers

Molecular Psychiatry 2012
Effects of Chronic Cannabis Exposure on Cannabinoid Receptor Density

- New CB-1 cannabinoid receptor ligand for PET studies, [18F]FMPEP-d2
- Collaboration with Bob Innis & Jussi Hirvonen of NIMH
- Imaged chronic daily cannabis smokers on admission to monitor CB1-cannabinoid receptor density
- Imaged chronic daily cannabis smokers after 30 days sustained abstinence
CB₁-Cannabinoid Receptors Specifically Downregulated in Cortical Regions of Chronic Daily Cannabis Smokers (N=30) as Compared to Controls (N=28)
CB₁ Cannabinoid Receptors Significantly Increased after Sustained Cannabis Abstinence (N=14)
Synthetic Cannabinoids Pharmacokinetics

- Teske et al 2010
  - 50µg/kg smoked JWH-018 to 1 M & 1 F
  - Serum collected 5 min to 48 h, LOD 0.07 µg/L
  - JWH-018 identified 5 min up to 48 h F, 24 h M

- Logan et al 2011
  - Smoked 3 puffs JWH-018 & JWH-073 within 30 min
  - Parent & metabolites identified 30 min (1st sample - 4h in blood)
Synthetic Cannabinoids
Pharmacokinetics

- Metabolism
  - Phase I (hydroxylation, carboxylation, dealkylation)
  - Phase II (glucuronidation)
  - Parent compound rarely found in urine
  - Critical to define metabolism of new designer drugs to permit identification of exposure
## Synthetic Cannabinoids in Human Biological Specimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Matrix</th>
<th>Concentration</th>
<th>Herbal Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM-2201</td>
<td>Femoral blood, Oral fluid, Serum</td>
<td>0.3 ng/g, 0.33 – 22 ng/mL, 9.5 ng/mL</td>
<td>Haze, Unknown, Unknown</td>
</tr>
<tr>
<td>AM-694</td>
<td>Femoral blood, Serum</td>
<td>0.09 ng/g, 0.20 ng/mL</td>
<td>Unknown, Sweed</td>
</tr>
<tr>
<td>JWH-015</td>
<td>Serum</td>
<td>&lt;10 ng/mL</td>
<td>Maya</td>
</tr>
<tr>
<td>JWH-018</td>
<td>Blood, Femoral blood, Hair, Oral Fluid, Serum</td>
<td>0.1 – 199 ng/mL, 0.05 ng/g, 5.1 – 5.7 pg/mg, 0.15–.53 ng/mL, 0.13 – 11 ng/mL</td>
<td>Unknown, Haze, Unknown, Unknown, K2 Summit, Smoke, Spice, Maya, Ninja</td>
</tr>
</tbody>
</table>
## Synthetic Cannabinoids in Human Biological Specimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Matrix</th>
<th>Concentration</th>
<th>Herbal Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-019</td>
<td>Oral Fluid</td>
<td>&lt;0.15 ng/mL, 11 ng/mL</td>
<td>Unknown, Unknown</td>
</tr>
<tr>
<td></td>
<td>Serum Serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JWH-072</td>
<td>Urine</td>
<td>111 ng/mL</td>
<td>Unknown</td>
</tr>
<tr>
<td>JWH-073</td>
<td>Blood CSF</td>
<td>0.1–68.3 ng/mL, 19 ng/mL</td>
<td>Unknown, Unknown</td>
</tr>
<tr>
<td></td>
<td>Hair Serum</td>
<td>0.7–21 pg/mg, 0.11–71 ng/mL</td>
<td>Unknown Maya</td>
</tr>
<tr>
<td>JWH-081</td>
<td>Blood Hair</td>
<td>1.2–42 ng/mL, 5.1–31 pg/mg</td>
<td>Jamaican Gold, Ninja Strong</td>
</tr>
<tr>
<td></td>
<td>Serum Serum</td>
<td>6 ng/mL</td>
<td>Unknown, Unknown</td>
</tr>
<tr>
<td>JWH-122</td>
<td>Serum</td>
<td>0.17–40 ng/mL</td>
<td>Monkees go bananas, Tropical car, Lava Red, &amp; others</td>
</tr>
<tr>
<td>JWH-210</td>
<td>Serum</td>
<td>0.20–190 ng/mL</td>
<td>Maya, Push, Bonzai Remix, Spice, Jamaican Gold</td>
</tr>
<tr>
<td>Drug</td>
<td>Matrix</td>
<td>Concentration</td>
<td>Herbal Product</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------</td>
<td>------------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>JWH-250</td>
<td>Hair</td>
<td>0.5–14 pg/mg</td>
<td>Unknown Monkees go bananas, Bonzai</td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>0.10–14 ng/mL</td>
<td></td>
</tr>
<tr>
<td>JWH-307</td>
<td>Serum</td>
<td>53 ng/mL</td>
<td>Unknown</td>
</tr>
<tr>
<td>MAM2201</td>
<td>Plasma</td>
<td>49 ng/mL</td>
<td>Samurai King</td>
</tr>
<tr>
<td>RCS-4</td>
<td>Serum</td>
<td>0.3 ng/mL</td>
<td>Unknown</td>
</tr>
<tr>
<td>JWH-018 N-pentanoic</td>
<td>Urine</td>
<td>11.6–11,182 ng/mL</td>
<td>Unknown</td>
</tr>
<tr>
<td>acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JWH-018 N-5-OH-pentyl</td>
<td>Urine</td>
<td>2.5–5,350 ng/mL</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Synthetic Cathinones

MDPV, Mephedrone, Butylone

1\textsuperscript{st} Generation Synthetic Cathinones

Phenyl ring substitution

Cathinone

3,4 methylenedioxy & pyrrolidinyl substitution

Mephedrone

3,4 methylenedioxy substitution

Methylvone

MDPV
2nd Generation Synthetic Cathinones

4-Fluoromethcathinone (4-FMC)

α-PVP

Pentedrone

Naphyrone, 3-FMC, Buphedrone, MDPPP, 4-MEC, Methedrone, Benzedrone, MDPBP, Ethylone, Butylone, & more!
Misuse of Synthetic Cathinones
Growing Public Health Concern

- 1st US poison control case in July 2010
- Within 1 year >4,000 cases reported
- >90% of cases in emergency departments
- Keto moiety typically less potent
- Pyrrolidophenones typically potent (MDPV)
- Longer the alkyl substituent lower the potency
Synthetic Cathinones

- Intranasal, injection & oral (dabbing, bombing) administration
- Doses vary with route & potency (5 mg – 5 g)
- Increase in designer cathinone use may be driven by lack of Ecstasy (Brundt et al., 2010)
Cocaine Blocks Dopamine Reuptake by Dopamine Transporter (DAT)
Amphetamine Enters Cell as DAT Substrate, Releasing Dopamine by Reverse Transport

Presynaptic dopamine cell

VMAT

Vesicles

DAT

Extracellular fluid

D2 or D3 receptor  Postsynaptic cell  D1 receptor
Designer Cathinones Interact with Monoamine Transporters

• Two types of interaction with transporters
  • Transporter blockers inhibit transmitter reuptake
  • Transporter substrates (i.e., releasers) enter cells & reverse normal direction of flux, cause transmitter release

• Drugs that interact with DAT are highly addictive
  • Cocaine is a DAT blocker
  • Amphetamine is a DAT substrate
Mechanisms of Action

- Mephedrone & methylone are substrates or monoamine releasers at transporters (like MDMA) *Baumann et al., 2012*
  - Dose-related increase in extracellular dopamine & serotonin (5-HT)
  - Methylone similar profile but ~ ½ as potent as mephedrone
- Pyrovalerone is dopamine transporter blocker (like cocaine) *Meltzer et al., 2006*
Mechanisms of Action

- MDPV potent dopamine & norepinephrine blocker (100X greater) than weak 5-HT effects
  - Surprising, due to 3,4-methylenedioxy group
  - Pyrovalerone has similar effects
  - Norepinephrine (NET) effects explain potential dangerous cardiovascular effects
  - MDPV inhibits dopamine clearance with higher potency & efficacy than cocaine (10-fold)
MDPV Potent Dopamine Uptake Blocker, Weaker Serotonin Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dopamine IC50, nM</th>
<th>5-HT IC50, nM</th>
<th>DA/5-HT ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDPV</td>
<td>4.4 ± 0.3</td>
<td>2556 ± 653</td>
<td>580</td>
</tr>
<tr>
<td>Mephedrone</td>
<td>765 ± 53</td>
<td>416 ± 29</td>
<td>0.5</td>
</tr>
<tr>
<td>Methylone</td>
<td>1684 ± 275</td>
<td>668 ± 144</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Baumann et al., 2012
MDPV Greater Potency & Efficacy than Cocaine for Inhibiting Dopamine Clearance

Baumann et al., 2012
MDPV Increases Dialysate Dopamine Levels in Rat Nucleus Accumbens

- MDPV at least 10-fold more potent than cocaine
- MDPV effects sustained compared to cocaine
MDPV Elicits Robust Dose-related Hyperactivity in Rats

• MDPV at least 10-fold more potent than cocaine
• MDPV more efficacious than cocaine
MDPV Increases Heart Rate & Blood Pressure in Rats More Than Cocaine

- MDPV at least 10-fold more potent than cocaine
- MDPV more efficacious than cocaine
Preclinical Cathinone Exposure

- Rapid onset of increased:
  - Locomotion
  - Heart rate
  - Blood pressure
  - Body temperature
  - Ataxia (3-FMC)
  - Convulsions (methylone)
  - Exploration (methylone, 3-FMC)
  - No dopamine neurotoxicity
Preclinical Cathinones Pharmacology

• Fantegrossi 2013
  - MDPV dosing to mice at warm temperatures
  - Potentiated motor activity,
  - Self-injurious behavior at high doses
  - Profound stereotypy
  - Only hyperthermic effects at warm temperatures; greater risk with drug use in warm environment
Preclinical Cathinones Pharmacology

- Mephedrone & methylone: no long lasting effects on brain monoamines but high doses cause selective brain serotonin depletion
- Preclinical locomotor & self-injurious behavior predict agitation, psychosis & violence in humans
- MDPV users prone to develop excited delirium, also seen in PCP users, possibly due to MDPV lipophilicity of & ability to cross BBB (Penders 2013)
Human Cathinone Exposure

- Effects similar to MAMP, cocaine & MDMA
- Phenethylamine core responsible for stimulatory effects
- Methylenedioxy group for empathogenic effect
  - Penders et al 2012
    - Low doses: euphoria & increased alertness
    - High doses: life threatening excited delirium, agitation, psychosis, hallucinations, tachycardia & death
    - Renal failure & skeletal muscle breakdown
Human Cathinone Effects

- Borek 2012
  - Multiorgan failure
- No human studies examining acute vs chronic cathinone exposure
### Emergency Room Symptoms 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>

Spiller et al., 2011
• Adult male shoots out windows of house while aiming at “strangers”
• Adult female, confused & agitated, leaves 2 year old child in middle of highway because child has “demons”
• Adult male jumps out of window to flee from non-existent “pursuers”
• Adult male breaks all windows in house & wanders barefoot through broken glass
Cathinone Pharmacokinetics

• No controlled human studies, but *in vivo* rat & *in vitro* human liver microsomes (HLM) & hepatocytes data

• Phase I (demethylenation, O-methylation, N-dealkylation, reduction of keto moiety)
  • CYP2D6, CYP2B6, CYP1A2, CYP2C19

• Phase II (glucuronidation & sulfation)
  • Unchanged parent compounds in urine at high concentrations, some conjugates
## Fatal Cathinone Concentrations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Matrix</th>
<th>µg/L</th>
<th>Other Drugs</th>
<th>Case</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butylone</td>
<td>Blood</td>
<td>22,000</td>
<td>ND</td>
<td>Suicide overdose</td>
<td>Rojek 2012</td>
</tr>
<tr>
<td>Mephedrone</td>
<td>Blood</td>
<td>5,500</td>
<td>ND</td>
<td>Fatality</td>
<td>Adamowicz 2013</td>
</tr>
<tr>
<td>Methylone</td>
<td>Heart blood</td>
<td>1,100</td>
<td>MDPV 30µg/L</td>
<td>Fatality</td>
<td>Cawrse 2012</td>
</tr>
<tr>
<td>Methylone</td>
<td>Peripheral blood</td>
<td>670</td>
<td>ND</td>
<td>Fatality</td>
<td>Cawrse 2012</td>
</tr>
<tr>
<td>Methylone</td>
<td>Peripheral blood</td>
<td>560</td>
<td>ND</td>
<td>Fatality</td>
<td>Pearson 2012</td>
</tr>
<tr>
<td>Methylone</td>
<td>Heart blood</td>
<td>111</td>
<td>ND</td>
<td>Fatality</td>
<td>Cawrse 2012</td>
</tr>
<tr>
<td>Drug</td>
<td>Matrix</td>
<td>µg/L</td>
<td>Other Drugs</td>
<td>Case</td>
<td>Ref.</td>
</tr>
<tr>
<td>----------</td>
<td>----------</td>
<td>---------</td>
<td>------------------------------</td>
<td>------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>MDPV</td>
<td>Blood</td>
<td>220</td>
<td>Opiates, Bupropion</td>
<td>Fatality</td>
<td>Microgram Nov 2012</td>
</tr>
<tr>
<td>MDPV</td>
<td>Heart blood</td>
<td>470</td>
<td>Methylone: 60µg/L</td>
<td>Fatality</td>
<td>Cawrse 2012</td>
</tr>
<tr>
<td>MDPV</td>
<td>Serum</td>
<td>670</td>
<td>ND</td>
<td>Fatality</td>
<td>Murray 2012</td>
</tr>
<tr>
<td>MDPV</td>
<td>Blood</td>
<td>16-8400</td>
<td>23% MDPV only</td>
<td>Driving</td>
<td>Kriikku 2011</td>
</tr>
<tr>
<td>MDPV</td>
<td>Blood</td>
<td>24-241</td>
<td>Not reported</td>
<td>Poison center</td>
<td>Spiller 2011</td>
</tr>
<tr>
<td>MDPPP</td>
<td>Serum</td>
<td>154</td>
<td>JWH-072:16 MDA:11µg/L</td>
<td>ED visit</td>
<td>Thorton 2012</td>
</tr>
<tr>
<td>Flephedrone</td>
<td>Serum</td>
<td>346</td>
<td>MDPV:</td>
<td>ED visit</td>
<td>Thorton 2012</td>
</tr>
</tbody>
</table>
Summary & Conclusions

- MDPV is primary synthetic cathinone found in US cases
- Could be due to improved stability
- MDPV produces observed adverse effects
- MDPV at least 10-fold more potent than cocaine *in vivo* at blocking dopamine uptake
- MDPV has unique pharmacology for cathinones
- Antagonism of excess DA signaling may aid in management of synthetic cathinone ED cases
A2 Blast Bolts BZP Cosmic Kelly ESP Euphoria Exodus Fast Lane Happy Pills Legal E Nemesis Party Pill

Synthetic Piperazines BZP, TFMPP, mCPP
Piperazine Structures

Benzylpiperazines

- 1-BZP
- MBZP
- 2C-B-BZP

Phenylpiperazines

- TFMPP
- mCPP
- MeOPP
Piperazines

- BZP developed in 1950’s to treat worms & 1970’s as anti-depressant
- Stopped due to amphetamine-like effects
- Recreational use 1st reported in 1990s
- BZP & TFMPP temporarily placed into Schedule I (2002)
- TFMPP removed from the list in 2004
- Both drugs often found in MDMA tablets
Piperazine Mechanisms of Action

- Stimulate release & inhibit reuptake of dopamine, serotonin & norepinephrine
- In animals, potency lower than d-AMP, d-MAMP & d-MDMA
- BZP effects are dose-related as it is both a partial agonist & antagonist at 5-HT receptor
- Little human data, but observed effects showed similar symptoms to MDMA exposure
Preclinical Piperazine Pharmacology

- BZP induced dose-dependent anxiety, locomotion & hyperactivity
- At high 10 mg/kg dose, BZP produced seizures in rats
- 0.13 – 0.5 mg/kg IV BZP substituted for 0.06 – 0.5 mg/kg cocaine in self-administration study in rhesus monkeys
- In drug discrimination studies, BZP substituted for amphetamines in rodents & primates
Preclinical Piperazine Pharmacology

- TFMPP alone did not increase locomotion
- TFMPP did not substitute for cocaine or amphetamines
- BZP & TFMPPP induced lower self-administration than BZP alone
Human Piperazine Pharmacodynamics

- Lin et al 2009
  - 200 mg BZP in 27 females
  - Similar effects
  - No pharmacokinetics samples
  - 200mg BZP vs placebo increased blood pressure, heart rate & feelings of self-confidence
Human Piperazine Pharmacodynamics

- Lin et al 2011
  - Randomized, double blind, N=36 males
  - Evaluated 2 h prior and after dosing
  - ARCI, VAS & POMS
  - No pharmacokinetics samples
  - 100/30mg BZP/TFMPP (single dose) vs placebo increased blood pressure, heart rate & feelings of self-confidence (similar to 200 mg BZP alone)
Human Piperazine Pharmacodynamics

- Thompson et al. 2010
  - Within-subject, cross-over design, 4 treatments
    - 300mg/74mg BZP/TFMPP & placebo alcohol
    - 300mg/74mg BZP/TFMPP & 57.6 g alcohol
    - Placebo piperazine & 57.6 g alcohol
    - Placebo piperazine & placebo alcohol
  - Evaluated driving performance & physiological effects
Human Piperazine Pharmacodynamics

- Only 35/64 subjects completed due to adverse events
  - 4/10 BZP/TFMPP only & 3/7 BZP/TFMPP with EtOH experienced adverse events
  - Agitation, anxiety, vomiting, insomnia, migraine, hallucinations, & increased BP & heart rate
  - No effects when placebo &/or EtOH only
Human Piperazine Pharmacodynamics

- BZP/TFMPP improved driving performance
  - Decreased standard deviation of lateral position (SDLP) 4.2 cm
- EtOH decreased driving performance when combined with BZP/TFMPP by increasing SDLP by 2.3 cm (non-significant increase)
Piperazine Pharmacokinetics

- Antia et al, *J For Science* 2010
  - 200 mg oral BZP: $C_{\text{max}}$ 262 µg/L, $T_{\text{max}}$ 75 min
    - Detectable in plasma < 30h
  - 60 mg oral TFMPP: $C_{\text{max}}$ 24.1 µg/L, $T_{\text{max}}$ 90 min
Piperazine Pharmacokinetics

**Metabolism/Elimination**

- Phase I (hydroxylation); metabolized by CYP2D6, CYP1A2 & CYP3A4
- Phase II (glucuronidation & sulfate conjugate)
- BZP major metabolites 3 & 4-OH-BZP, O & N-BZP-sulfate found in urine for more than 24 h
- TFMPP has two half-lives 2.0 & 6.0 h
- TFMPP metabolites 4-OH-TFMPP
Piperazine Pharmacokinetics

• Metabolism/Elimination
  • mCPP is a metabolite of trazodone, nefazodone, enziprazole & etoperidone
  • When mCPP ingested, p-OH-mCPP metabolite detected in blood, plasma, urine
Piperazine Fatalities

- Elliot et al 2011
  - BZP postmortem: 0.5 – 1.4 mg/L (femoral blood); 4.9 - 15.7 mg/L (urine)
  - TFMPP postmortem: 0.05 – 0.15 mg/L (femoral blood); 0.9 – 1.0 mg/L (urine)
  - Other drugs reported: benzodiazepines, cocaine, ketamine, amphetamine &/or EtOH
• BZP is a more potent stimulant than TFMPP
• BZP & TFMPP improved driving performance at low doses, but produced adverse effects such as agitation, anxiety, hallucinations, insomnia, & migraine
• Need more pharmacokinetic data on mCPP
Synthetic Hallucinogens
Tryptamines (5-MeO-DiPT, Foxy) & Phenethylamines (DOM, 2C-B)
Phenylethylamines
I Have Known & Loved
by Alexander & Ann Shulgin
1991
Phenethylamine 2C Structures

2,5-dimethoxyphenethylamine (2C-H)

2C-B (R4: Br)
2C-C (R4: Cl)
2C-D (R4: CH₃)
2C-E (R4: CH₂CH₃)
2C-I (R4: I)
2C-N (R4: N₂O)
2C-P (R4: CH₂CH₂CH₃)
2C-T (R4: S)
2C-T2 (R4: S-CH₂CH₃)
2C-T4 (R4: S-isopropyl)
2C-T7 (R4: S-propyl)
Shulgin synthesized >200 psychoactive compounds in his laboratory at UCSF.

Book covers synthesis, bioassay, dosages & effects.

Synthetic Drug Abuse & Prevention Act 2012

Nine 2C on Schedule I
2C Mechanisms of Action

- Little data on pharmacological & toxicological properties of 2C series
- Have affinity to 5-HT$_2$ receptors & act as agonists or antagonists at different receptor subtypes
2C Pharmacology

Clinical Effects  Dean et al. 2013 *J Med Tox*

- Route of administration: oral, insufflation
- Hallucinations, euphoria, empathy, nausea, vomiting, agitation, tachycardia, hypertension, respiratory depression & delirium, seizures, psychosis & suicidal thoughts
- Excited delirium: delirium with agitation → violence
- Hyperactivity → hyperthermia → cardiopulmonary arrest
- 2C intoxication & overdose reported
<table>
<thead>
<tr>
<th>2C</th>
<th>Chemical Name</th>
<th>Dosage mg</th>
<th>Duration h</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C-B</td>
<td>4-Bromo-2,5-dimethoxyphenethylamine</td>
<td>12–24</td>
<td>4–8</td>
</tr>
<tr>
<td>2C-C</td>
<td>4-Chloro-2,5-dimethoxyphenethylamine</td>
<td>20–40</td>
<td>4–8</td>
</tr>
<tr>
<td>2C-D</td>
<td>4-Methyl-2,5-dimethoxyphenethylamine</td>
<td>20–60</td>
<td>4–6</td>
</tr>
<tr>
<td>2C-E</td>
<td>4-Ethyl-2,5-dimethoxyphenethylamine</td>
<td>10–25</td>
<td>8–12</td>
</tr>
<tr>
<td>2C-G</td>
<td>3,4-Dimethyl-2,5-dimethoxyphenethylamine</td>
<td>20–35</td>
<td>18–30</td>
</tr>
<tr>
<td>2C-G-3</td>
<td>3,4-Trimethylene-2,5-dimethoxyphenethylamine</td>
<td>16–25</td>
<td>12–24</td>
</tr>
<tr>
<td>2C-G-5</td>
<td>3,4-Norbornyl-2,5-dimethoxyphenethylamine</td>
<td>10–16</td>
<td>32–48</td>
</tr>
<tr>
<td>2C-I</td>
<td>4-Iodo-2,5-dimethoxyphenethylamine</td>
<td>14–22</td>
<td>6–10</td>
</tr>
<tr>
<td>2C-N</td>
<td>4-Nitro-2,5-dimethoxyphenethylamine</td>
<td>100–150</td>
<td>4–6</td>
</tr>
<tr>
<td>2C-P</td>
<td>4-Propyl-2,5-dimethoxyphenethylamine</td>
<td>6–10</td>
<td>10–16</td>
</tr>
<tr>
<td>2C</td>
<td>Chemical Name</td>
<td>Dosage mg</td>
<td>Duration h</td>
</tr>
<tr>
<td>------</td>
<td>---------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>2C-SE</td>
<td>4-Methylseleno-2,5-dimethoxyphenethylamine</td>
<td>~100</td>
<td>6–8</td>
</tr>
<tr>
<td>2C-T</td>
<td>4-Methylthio-2,5-dimethoxyphenethylamine</td>
<td>60–100</td>
<td>3–5</td>
</tr>
<tr>
<td>2C-T-2</td>
<td>4-Ethylthio-2,5-dimethoxyphenethylamine</td>
<td>12–25</td>
<td>6–8</td>
</tr>
<tr>
<td>2C-T-4</td>
<td>4-Isopropylthio-2,5-dimethoxyphenethylamine</td>
<td>8–20</td>
<td>12–18</td>
</tr>
<tr>
<td>2C-T-7</td>
<td>4-Propylthio-2,5-dimethoxyphenethylamine</td>
<td>10–30</td>
<td>8–15</td>
</tr>
<tr>
<td>2C-T-8</td>
<td>4-Cyclopropylmethylthio-2,5-dimethoxyphenethylamine</td>
<td>30–50</td>
<td>10–15</td>
</tr>
<tr>
<td>2C-T-9</td>
<td>4-(t)-Butylthio-2,5-dimethoxyphenethylamine</td>
<td>60–100</td>
<td>12–18</td>
</tr>
<tr>
<td>2C-T-13</td>
<td>4-(2-Methoxyethylthio)-2,5-dimethoxyphenethylamine</td>
<td>25–40</td>
<td>6–8</td>
</tr>
<tr>
<td>2C-T-15</td>
<td>4-Cyclopropylthio-2,5-dimethoxyphenethylamine</td>
<td>&gt;30</td>
<td>Few h</td>
</tr>
<tr>
<td>2C-T-17</td>
<td>4-(s)-Butylthio-2,5-dimethoxyphenethylamine</td>
<td>60–100</td>
<td>10–15</td>
</tr>
</tbody>
</table>
2C-B metabolism by human hepatocytes.

Meyer & Maurer, *Current Drug Metabolism* 2010.
2C Metabolism

- Meyer & Maurer Current Drug Metabolism 2010
  - Primarily O-demethylation in position 2 or 5 of aromatic ring &/or reduction to alcohol
  - 2Cs containing sulfur undergo sulfoxidation
  - Monoamine oxidases (MAO-A & MAO-B) important for deamination
  - Phase II: glucuronidation &/or sulfation
# 2C Deaths

<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 y M</td>
<td>2C-T-7</td>
<td>Snorted</td>
<td>35 mg</td>
<td>Vomiting, hallucinations, agitation, aggression, nasal bleeding, possible seizure activity, pulmonary edema, cardio/pulmonary arrest</td>
</tr>
<tr>
<td>17 yr M</td>
<td>2C-T-7</td>
<td>Snorted</td>
<td>?</td>
<td>Agitation, violence, aggression, possible hyperthermia (removal of clothing), rigidity, cardio-pulmonary arrest</td>
</tr>
<tr>
<td>Age ? M</td>
<td>2C-T-7 &amp; MDMA</td>
<td>?</td>
<td>? 2CT-7; 200 mg MDMA</td>
<td>Agitation, aggression, violence, seizures, hallucinations, cardio/pulmonary arrest, cerebral hemorrhage</td>
</tr>
<tr>
<td>Age/sex</td>
<td>Agent</td>
<td>Route</td>
<td>Dose</td>
<td>Symptoms</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>-----------</td>
<td>------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>19 y M</td>
<td>2C-E</td>
<td>Snorted</td>
<td>?</td>
<td>Aggressive/agitation, hyperthermia, DIC, multi-organ failure</td>
</tr>
<tr>
<td>17 y M</td>
<td>2C-I-NBOMe</td>
<td>Oral</td>
<td>?, mixed with chocolate</td>
<td>Hyperventilation, foaming at mouth</td>
</tr>
<tr>
<td>18 y M</td>
<td>2C-I-NBOMe</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>22 y M</td>
<td>2C-T-21</td>
<td>Oral</td>
<td>? dipped tongue into powder</td>
<td>Hyperthermia (108 °C), seizures, coma</td>
</tr>
</tbody>
</table>
Summary

- Phenethylamines 2C series produce effects similar to Ecstasy
- Human pharmacokinetic data limited
- 2C-B metabolism produces multiple metabolites in human hepatocytes
Tryptamines I Have Known & Loved
Tryptamines

* Not DEA scheduled
Tryptamines

- Tryptamines produce hallucinations in humans
- Endogenous tryptamines are derived from tryptophan & converted via biological pathways
- High affinity for 5-HT$_2$ serotonin receptors
- Little binding affinity data available for synthetic tryptamines
- Only 5-MeO-DiPT studied in rodent brain
Tryptamines

• 5-MeO-DiPT one of 25 most frequently identified drugs, increased 36-fold between 2010-2011 (NFLIS)
• Tryptamines Schedule I in 2004
• Psilocybin, a natural occurring tryptamine, is converted to psilocin (also Schedule I)
• Often found with BZP, TFMPP, MDMA & synthetic cathinones
• LSD is considered part of tryptamine family
Tryptamines Pharmacology

- Administered orally, insufflation & smoking
- Self-reported human effects (Shulgin, 1997)
  - Entheogenic (feeling divine within), euphoric, sensual, visual hallucinations, “out of body” experience, reduced limb control, nausea, anxiety, bruxism, dilated pupils, tachycardia, headache & sweating
- Subjective effects reported within 30 min, peak 1 – 1.5 h, duration 3 – 6 h
Preclinical Tryptamines Pharmacology

- Fantegrossi *Biochemistry & Behavior* 2006
  - 0.3 – 10 mg/kg ip dose to rats induced dose-dependent head-twitch-response
  - 5-MeO-DiPT > DMT > control
  - 30 mg/kg induced convulsions
  - 5-MeO-DiPT produced LSD-like discriminative stimulus effects
5-MeO-DiPT Pharmacokinetics
Meyer & Maurer *Current Drug Metabolism* 2010

5-MeO-DiPT

CYP2D6

CYP1A1

CYP1A2

CYP2C9/19

CYP3A4

6-OH-5-MeO-DiPT

5-OH-DiPT

5-MeO-IPT
Tryptamines Pharmacokinetics

- Shen et al *Biochemical Pharmacology* 2010
  - 5-MeO-DMT pharmacokinetics from human liver microsomes, hepatocytes & *in vivo* studies in rats
  - Phase I metabolism *O*-demethylation for 5-MeO-DMT
  - After IV & IP administration in rat blood 5-MeO-DMT shows nonlinear pharmacokinetics
  - Phase II: not characterized
Tryptamines Pharmacokinetics

- 5-MeO-DiPT pharmacokinetic studies in human & rat liver microsomes, \textit{in vivo} rat studies
- 5-MeO-DiPT Phase I metabolism primarily \textit{O}-demethylation & hydroxylation; side chain \textit{N}-dealkylation
- Phase II: glucuronidation & sulfation
- Limited pharmacokinetics for other designer tryptamines
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