Inhalants, Club Drugs and Hallucinogens
Conflicts

- Paid consultant Reckitt-Benckiser
- Grant support form NIDA
- Open to more
Outline for today

- Overview
  - Epidemiology
- Inhalants
  - Solvents, \( N_2O \)
- Club Drugs
  - MDMA
- Hallucinogens
  - LSD, Psilocybin, *Salvia Divinorum*
Abuse of inhalants and hallucinogens is small relative to many drugs but is more than heroin.

Club drugs may no longer be a relevant term.
2002-2008 Past Month Use in Kids 12 to 17

- Illicit Drugs
- Psychotherapeutics
- Marijuana
- Inhalants
- Hallucinogens

Percent Using in Past Month

2002: 11.6%
2003: 11.2%
2004: 10.6%
2005: 9.9%
2006: 9.8%
2007: 9.5%
2008: 9.3%

NSDUH 2009
Initiation of Drug Use – all ages

- Marijuana (56.6%)
- Pain Relievers (22.5%)
- Inhalants (9.7%)
- Tranquilizers (3.2%)
- Hallucinogens (3.2%)
- Stimulants (3.0%)
- Cocaine (0.8%)
- Sedatives (0.8%)
- Heroin (0.1%)

2.9 Million Initiates of Illicit Drugs

NSDUH 2009
How Many Start Using MDMA, Inhalants or Hallucinogens?

<table>
<thead>
<tr>
<th>Substance</th>
<th>Numbers in Thousands</th>
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<tbody>
<tr>
<td>Marijuana</td>
<td>2,208</td>
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<tr>
<td>Pain Relievers</td>
<td>2,176</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>1,127</td>
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<tr>
<td>Inhalants</td>
<td>894</td>
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<tr>
<td>Cocaine</td>
<td>729</td>
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<tr>
<td>Stimulants</td>
<td>722</td>
</tr>
<tr>
<td>LSD</td>
<td>599</td>
</tr>
<tr>
<td>Sedatives</td>
<td>394</td>
</tr>
<tr>
<td>Heroin</td>
<td>181</td>
</tr>
<tr>
<td>PCP</td>
<td>114</td>
</tr>
</tbody>
</table>

NSDUH 2009
How old are your kids?

The image shows a bar chart from the NSDUH 2009 report, indicating the average age in years at which various substances are used by kids. The substances listed are PCP, Inhalants, Marijuana, LSD, Cocaine, Ecstasy, Pain Relievers, Stimulants, Sedatives, Heroin, and Tranquilizers. The ages range from 15.8 to 24.4 years.
Inhalant Abuse

- The deliberate inhalation or sniffing of common products to get high
- More than 1000 items can be abused:
  - **Solvents** - Acetone, benzene, difluoroethane, ethanol, ethyl acetate, hexane, methanol, methylene chloride, naptha, toluene, trichloroethane, trichlormethane
  - **Fuels** - Butane, gasoline, kerosene, propane
  - **Aerosols/Gases** - flurocarbons, Freon, helium, xenon
  - **Nitrates** - Amyl Nitrate (poppers), Butyl Nitrate (Rush, Locker Room, Climax)
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Some Abusable Products

- **Adhesives**: Model airplane glue, Rubber cement, PVC cement
- **Aerosols**: Spray paint, Hairspray, Air freshener, Deodorant, Fabric protectors
- **Cleaning Agents**: Dry cleaning fluid, Spot removers, Degreaser
- **Food Products**: Whipped cream Whippets
- **Gasses**: Nitrous oxide, Butane, Propane, Helium
- **Solvents and Gases**: Nail polish remover, Paint thinner, Paint remover, Correction fluid and thinner, Toxic magic markers, Pure toluene, Cigar lighter fluid, Gasoline, Carburetor cleaner, Octane booster, Fuel gas, Air Conditioning Coolant (Freon), Lighters, Fire Extinguishers
'Climax' brand Amyl Nitrite
Photo by Scott Murray, © 2001 Erowid.org
Methods of Abuse

- **Huffing and sniffing**
  - Taken directly from container into nose (sniffing) or from soaked rag held to face or stuffed in mouth (huffing)

- **Bagging**
  - Inhaled from closed bag
  - Risk of suffocation if bag gets stuck on the head

- **Balloons**
  - Popular with N\textsubscript{2}O
  - Risk of asphyxiation due to 100% N\textsubscript{2}O, 0% O\textsubscript{2}
Huffing - Bagging - Sniffing

Is communication with your kids BROKEN?

Talk to them about the dangers of INHALANT ABUSE

www.inhalant.org

Designee #7203
Combined Federal Campaign
Users - Who and Why

- In 2008 729,000 persons aged 12 and older used an inhalant for the 1st time

<table>
<thead>
<tr>
<th></th>
<th>Lifetime</th>
<th>Past Year</th>
<th>Past Month</th>
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<tbody>
<tr>
<td>NSDUH</td>
<td>10.4%</td>
<td>1.6%</td>
<td>0.3%</td>
</tr>
<tr>
<td>MTF</td>
<td>8.4%</td>
<td>1.7%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

- 70% of users are under age 18
- Consistently highest in 8th Graders
- Probably because drugs are
  - Legal to buy and posses
  - Readily accessible in the home
  - Inexpensive of free
Use declines as you get older

2009 Monitoring the Future
Despite disapproval
Nitrous Oxide

- Dissociative anesthetic gas
- Easily available
  - Dental offices, whipped cream propellants
  - Medical gas supplied in blue cylinders
- Pharmacology:
  - Directly depresses CNS ventilatory centers and myocardial function
  - Not a muscle relaxant
  - Not a trigger for malignant hyperthermia
Respiratory depression, apnea, diffusion hypoxia, cold gas can freeze lips, nose and vocal cords

Hypoxia from displacement of $O_2$
- Breathing from masks or in closed spaces (pick up cabs)
- Diffuses into air containing spaces 34 times faster than N

Hypotension, arrhythmias

Dizziness, euphoria, increased cerebral blood flow leading to increased intracranial pressure, neuropathy with chronic exposure (? $B_{12}$ associated)

Nausea, vomiting, ileus

Bone marrow suppression with chronic use, malignant hyperthermia
Nitrous Hardware

[Image of various nitrous oxide hardware components, including a Reddi-wip canister and an ISI cream charger box.]
Club Drugs
Club Drugs - What Are They

- Drugs people take while going to nightclubs, music festivals, raves and dance parties.
- Used to enhance social intimacy and sensory stimulation
Usual Suspects

- MDMA (Ecstasy), GHB, LSD, Ketamine, Methamphetamine
- For some reason Ethanol and Cannabis not included
- No major new agents in the last few years
  - May need new music before new drugs emerge
Club Drugs - Why and How

- Low cost
  - $5.00 to $20.00 per intoxication
- Convenient distribution as small pills, powders, or liquids
- Usually are:
  - Taken orally
  - May be taken in combination with each other, with alcohol, or with other drugs
Emergence of new abused drugs

- Emergence of new drugs into the illicit marketplace is an important public health event
- Some top the charts with a bullet:
  - MDMA, Methamphetamine
- Some find a niche
  - GHB, phencyclidine, mescaline, psilocybin, ketamine
- Others never achieve their ‘potential’
  - methcathinone
Factors affecting success - Why some ‘succeed and some ‘fail’:

- New compounds often not illegal
- Amenable to commerce, readily manufactured
Identity and purity

- Often are adulterated or misrepresented
- Any club drug overdose should be assumed as polydrug use with the actual substance and dose unknown.
- Toxicological screening generally is not available for many club drugs
  - GHB, Ketamine
Structure and Related Compounds

- MDMA is a phenethylamine
  - 3,4 methylenedioxyamphetamine
- Closely related to the Amphetamines
- Not new drugs:
  - MDMA patented by Merck in 1914
  - Amphetamine first synthesized in 1887 in Germany
  - Methamphetamine first synthesized in 1919 in Japan
Abused Phenethylamines

MDMA

Methamphetamine

Mescaline
Therapeutic Phenethylamines

Phenylephrine

Terbutaline
Catechol Phenethylamines

Dopamine

Epinephrine

Dobutamine
Prazosin-MDMA Interactions
Why study Noradrenergic effects of MDMA?
Data from Verrico et al. 2007. Human embryo kidney (HEK)-293 cells were stably transfected with the human DAT, NET, or SERT and preloaded with [3H]DA, [3H]NE, and [3H]5-HT respectively. Han and Gu (2006) reported that the potency of MDMA to inhibit monoamine release at human transporters was NET (KI = 1.19 μM), SERT (KI = 2.41 μM), and DAT (KI = 8.29 μM).

(Steele et al. 1989; Lavelle et al. 1999; Rothman et al. 2001; Fitzgerald and Reid 1993).

ND = None detectable
Alpha₁-adrenoceptors in ventral tegmental area and prefrontal cortex modulate striatal dopamine release \((\text{Pan et al.}, 1996; \text{Shi et al.}, 2000)\)

This dopamine release is considered important for the addictive properties of drugs.

Norepinephrine release has also been suggested to contribute directly to euphoric effects of stimulants \((\text{Rothman et al.} 2001; \text{Leyton et al.} 2007)\)
Prazosin

- Prazosin is an alpha-1 noradrenergic inverse agonist
- Used clinically to treat hypertension
Why use Prazosin?
Prazosin is an old, well-understood drug. It enters the brain (Menkes et al. 1981). Typically has few pharmacokinetic interactions. Has been studied with MDMA in animals (Fantegrossi et al. 2004; Selkin and Nichols 2007).

For example, Selkin and Nichols (2007) found it reduces the locomotor effect of MDMA in rodents:
Study Design

- Double-blind, placebo-controlled within-subjects study
- Sixteen healthy, MDMA-experienced participants (8 male, 8 female) participated in four sessions:
  - Double placebo
  - 1.5 mg/kg PO MDMA
  - 1-2 mg PO prazosin
  - 1-2 mg PO prazosin followed 1 hr later by 1.5 mg/kg PO MDMA (‘Combo’)

Physiological effects
- Heart rate
- Diastolic blood pressure
- BDNF

Self-report effects
- Pleasurable and unpleasurable effects (SDEQ)
- Sociability (IASR)

Categorization of Emotions task
Hypothesis

- MDMA will have typical stimulant effects, increasing blood pressure and euphoria
- MDMA will have unusual emotional effects, increasing sociability and altering recognition of emotional expressions
- Prazosin will attenuate the typical stimulant effects of MDMA without reducing the unusual emotional effects of MDMA
Results
Heart Rate

**Effect vs. Time**

- Time (hours): 0, 20, 40, 60
- Heart Rate (bpm): -0.25, 1, 2, 3, 4, 6, 8

- Placebo
- MDMA
- Prazosin
- Combo

**Emax**

- Placebo
- MDMA
- Prazosin
- Combo

**AUC**

- Placebo
- MDMA
- Prazosin
- Combo

Prazosin (or placebo) is at minus 1 hr.
MDMA (or placebo) is at 0 hr.

Measures are expressed as change from minus 2 hr baseline.
Emax is maximum change from baseline for each individual.

Heart Rate

Effect vs. Time

Emax

AUC

Placebo
MDMA
Prazosin
Combo

0 50 100 150 200

0 20 40 60

-0.25 1 2 3 4 6 8

Time (hours)

Heart Rate (bpm)
Heart Rate

Effect vs. Time

- Placebo
- MDMA
- Prazosin
- Combo

AUC is the Area Under the effect-vs-time Curve
**MDMA increases Heart**

**Effect vs. Time**

- **Emax**: Main effect of Condition $F(3, 45) = 39.39$, $P < .0001$
- **AUC**: Main effect of Condition $F(3, 45) = 24.95$, $P < .0001$

* $Emax: T = 4.38, P = .0001$; **AUC**: $T = 4.81, p < .0001$
**Combo further increases this effect**

- **Emax**: \( T = 4.38, \ P = .0001 \)
- **AUC**: \( T = 3.01, \ p < .0043 \)

* Graphs showing changes in heart rate over time for Placebo, MDMA, Prazosin, and Combo conditions.*
Diastolic Blood Pressure

Effect vs. Time

Emax

AUC
MDMA increases Diastolic BP

**Effect vs. Time**

Emax: Condition F (3, 45) = 25.15, P < .0001
AUC: Condition F (3, 45) = 31.06, P < .0001

Emax: T = 6.38, P < .0001
AUC: T = 6.29, p < .0001
Combo decreases this effect

**Effect vs. Time**

![Graph showing diastolic blood pressure changes over time with different conditions: Placebo, MDMA, Prazosin, and Combo.](image)

**Emax**

- **Emax:** Condition F (3, 45) = 25.15, P < .0001

**AUC**

- **AUC:** Condition F (3, 45) = 31.06, P < .0001

* Emax: T = 3.24, P = .0022
  
* AUC: T = 3.81, p = .0004
Visual analog ‘good drug effect’
Drug interactions not significant on most visual analog questions
SDEQ was developed by Katz and Waskow (1968) to measure effects of LSD and d-amphetamine.

Has subscales sensitive to the pleasurable and unpleasurable effects of stimulants.
Main effect of Condition
F (3, 172) = 16.21842
P < .0001
Combo decreases pleasurable MDMA effects

Main effect of Condition
F (3, 172) = 16.21842
P <.0001

* p = 0.028
Pleasurable effect subscales

SDEQ "Euphoria"

Placebo
MDMA
Prazosin
Combo

Mood
Functioning
Somatic
Pleasurable effect subscales

Functioning
T = 1.946
p = 0.053

Mood
T = 2.205
p = 0.029 *

Somatic
T = 1.891
p = 0.060
MDMA has unpleasurable effects

Main effect of Condition
F(3, 172) = 7.593
P <.0001
Main effect of Condition
$F(3, 172) = 7.593$
$P < .0001$

NS $p = .3030$

Combo doesn’t alter unpleasuable effects
IASR (Wiggins, Trapnell, & Phillips 1988) is a widely-used 64 item self-report questionnaire measuring interpersonal traits (items include: crafty, cheerful, warm)

One of its two main scales measures sociability
MDMA increases Sociability

* p=.0011
Combo does not affect this Sociability
IASR Sociability was increased by MDMA

This is first time unusual social effects of MDMA have been demonstrated with a validated instrument in a clinical study
BDNF mediates neuroplasticity
Decreased in many CNS diseases
Increases associated with improvement
Physiological and self-report effects of MDMA:

- MDMA produced typical stimulant effects (increased blood pressure, heart rate, & pleasurable subjective effects)
  - Altered by coadministration of prazosin
- MDMA had increases in sociability
  - Not significantly altered by coadministration of prazosin.
Can everyone safely tolerate MDMA?
Maximum Pulse after MDMA

N = 50
1.5 mg/kg MDMA
Maximum Systolic BP after MDMA

N = 50
1.5 mg/kg MDMA

Cut-off for further doses
Maximum Diastolic BP after MDMA

N = 50
1.5 mg/kg MDMA

Cut-off for further doses
Hyponatremia is a reported complication of illicit MDMA use

- Hyponatremia = Low sodium in blood (below 130 mmol/L)
- Signs and symptoms include headache, muscle cramps, confusion, seizures, death.
- Significant risk of mortality when it rapidly develops.
- Found in 13% of MDMA-related cases reported to the California Poison Control System from 2000-2005 (Robinson et al. 2007)
# Published series of MDMA-related hyponatremia cases

Table 1. Clinical Characteristics and Outcome of Patients with MDMA-Associated Hyponatremia

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>No. of Pills</th>
<th>Water Intake</th>
<th>Temperature (°C)</th>
<th>Sodium (mmol/L)</th>
<th>Osmolality (mOsm/kg)</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>F</td>
<td>3</td>
<td>NA</td>
<td>“normal”</td>
<td>120/186</td>
<td>242/562</td>
<td>HS, Fr, WR</td>
<td>Recovery</td>
<td>14</td>
</tr>
<tr>
<td>27</td>
<td>F</td>
<td>2</td>
<td>“copious amounts”</td>
<td>NA</td>
<td>124/NA</td>
<td>267/NA</td>
<td>Fr</td>
<td>Death</td>
<td>15</td>
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<tr>
<td>26</td>
<td>M</td>
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<td>NA</td>
<td>101/NA</td>
<td>248/NA</td>
<td>Fr, NS</td>
<td>Recovery</td>
<td>16</td>
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<tr>
<td>17</td>
<td>F</td>
<td>1</td>
<td>“several liters”</td>
<td>37.5</td>
<td>115/10</td>
<td>256/577</td>
<td>NS</td>
<td>Recovery</td>
<td>17</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>NA</td>
<td>NA</td>
<td>35.9</td>
<td>115/162</td>
<td>253/522</td>
<td>HS, Fr</td>
<td>Recovery</td>
<td>18</td>
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<tr>
<td>24</td>
<td>F</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>113/153</td>
<td>240/639</td>
<td>WR</td>
<td>Recovery</td>
<td>19</td>
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<tr>
<td>20</td>
<td>F</td>
<td>1/2</td>
<td>NA</td>
<td>“normal”</td>
<td>119/145</td>
<td>263/491</td>
<td>WR, NS</td>
<td>Recovery</td>
<td>20</td>
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<tr>
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<td>1</td>
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<td>34</td>
<td>117/1</td>
<td>38/NA</td>
<td>NA, NA</td>
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<td>21</td>
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<tr>
<td>15</td>
<td>F</td>
<td>NA</td>
<td>“large quantities”</td>
<td>32.8</td>
<td>125/NA</td>
<td>NA/NA</td>
<td>NS, WR, Fr</td>
<td>Death</td>
<td>22</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>1</td>
<td>“large quantity”</td>
<td>“normal”</td>
<td>112/112</td>
<td>238/256</td>
<td>Mannitol</td>
<td>Recovery</td>
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<td>256/655</td>
<td>WR</td>
<td>Recovery</td>
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<td>16</td>
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<td>NA</td>
<td>112/99</td>
<td>242/184</td>
<td>WR</td>
<td>Recovery</td>
<td>23</td>
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<tr>
<td>24</td>
<td>F</td>
<td>1</td>
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<td>38</td>
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<td>258/365</td>
<td>HS</td>
<td>Recovery</td>
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<td>F</td>
<td>1</td>
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<td>35</td>
<td>121/111</td>
<td>242/485</td>
<td>HS</td>
<td>Recovery</td>
<td>27</td>
</tr>
</tbody>
</table>

*F, female; M, male, NA, not available; HS, hypertonic saline; NS, normal saline; Fr, furosemide; WR, water restriction.*
MDMA-related hyponatremia occurs with relatively modest doses

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</table>

F, female; M, male; NA, not available; HS, hypertonic saline; NS, normal saline; Fr, furosemide; WR, water restriction.
## MDMA-related hyponatremia mostly affects Females

### Table 1. Clinical Characteristics and Outcome of Patients with MDMA-Associated Hyponatremia

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<tr>
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</table>

*F, female; M, male; NA, not available; HS, hypertonic saline; NS, normal saline; Fr, furosemide; WR, water restriction.*
Excessive water intake may sometimes play a role

Table 1. Clinical Characteristics and Outcome of Patients with MDMA-Associated Hyponatremia

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>No. of Pills</th>
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</table>

F, female; M, male; NA, not available; HS, hypertonic saline; NS, normal saline; Fr, furosemide; WR, water restriction.
MDMA tends to decrease serum sodium

N = 16
1.5 mg/kg MDMA
Limited water allowed
MDMA tends to increase antidiuretic hormone

N = 16
1.5 mg/kg MDMA
Limited water allowed
But it isn’t the same people!

N = 16
1.5 mg/kg MDMA
Limited water allowed
No obvious relationship between ADH and serum sodium

- We find no evidence that ADH changes are driving serum sodium decreases.
- Does not support the hypothesis that MDMA causes a Syndrome of Inappropriate ADH Secretion (SIADH)
o-8 Hr Urine Volumes

Urine Volume (0 to 8 Hr, mL)
0-8 Hr Urine Volumes

Urine Volume (0 to 8 Hr, mL)
Decrease expected if MDMA induces inappropriate antidiuretic hormone secretion.
MDMA increased Urine Output

Urine Volume (0 to 8 Hr, mL)
Does not support the hypothesis that MDMA causes a Syndrome of Inappropriate ADH Secretion (SIADH)
We used 2D echo to assess cardiovascular profiles of MDMA.

Compared cardiovascular effects to a known cardiostimulant — Dobutamine.

Hypothesized MDMA would produce similar CV effects to modest dose of Dobutamine.
Non-invasive method to measure cardiac cavity size, wall motion, wall thickness, and pressure gradients across valves
- Can measure stroke volume and ejection fraction
- Can calculate cardiac output and wall stress
Well defined clinical protocol for stress test

Produces cardiac beta receptor stimulation with increased heart rate but decreased blood pressure

Requires a single 40 minute test session to define dose response curve
Dobutamine Doses

- Ascending dose protocol:
  - 5 µg/kg/min for 3 minutes then
  - 20 µg/kg/min for 3 minutes then
  - 40 µg/kg/min for 3 minutes then stop
Effects of Dobutamine and MDMA on Heart Rate

![Graph showing heart rate responses to different doses of Dobutamine and MDMA.](chart.png)
Effects of Dobutamine and MDMA on Cardiac Output

![Graph showing the effects of Dobutamine and MDMA on cardiac output. The x-axis represents different doses of Dobutamine and MDMA, ranging from 0 to 40 mcg/kg for Dobutamine and 0 to 1.5 mg/kg for MDMA. The y-axis represents cardiac output in liters per minute, ranging from 2 to 10 L/minute. The graph illustrates that higher doses of Dobutamine and MDMA generally increase cardiac output.]
Effects of Dobutamine and MDMA on Wall Stress/Ejection Fraction
No effect on end systolic or diastolic stroke volume
- Increased cardiac output by 2 L/min over baseline (a rate effect)
- In contrast to Dobutamine, no direct inotropic effects
- However, MDMA increased wall stress
MDMA - Hysteresis

The clockwise hystereses shown above indicate peak subjective ratings.
Plasma Concentration remains relatively constant from 2 to 5 hours post dose.
But Intoxication falls from ~50 to 10 over the same time period.
Will MDMA ever be a medication?

- Reasons why not:
  - Abused by millions
  - Hypertension and Hyponatremia (and other AEs) suggests a substantial safety risk
    - Low tolerance by the public for prescription medications that can cause harm
- Reasons why:
  - Unique set of effects
  - May need only one at most a few doses
Thoughts on how MDMA could become an accepted therapeutic

- Multiple, repeat treatments with MDMA unlikely
- Not typical Psychiatric model
  - No weekly MDMA sessions
  - Responses occur immediately, not over years
Surgeon responsible for operation
Anesthesiologist responsible for the patient
Essential requirements for successful surgery:
- Proper case selection
- Adequate pre op preparation
- Careful monitoring during surgery
- Ability to manage complications in the OR
- Post operative procedures that assure safe recovery
How would this work for MDMA?

- Evaluate and select only those cases with a high probability of a good response
- Full medical work up before dosing
- Doses given in settings where medical help can respond and intervene
- Dedicated physician to monitor physiologic and psychiatric response during and after MDMA
- Proper training and certification of the entire team
Hallucinogens
Psychoactive drugs that alter perception, mood and a host of cognitive processes.
Do not produce ‘true’ hallucinations
Hallucinogens are

- Classically drugs that stimulate the 5-HT$_{2A}$ receptor
  - Tryptamines
  - Phenethylamines
- But also a pharmacological catchall term
  - Includes cannabinoids, NMDA antagonists, anticholinergic agents, Salvia Divinorum
Hallucinogen Structures

- **DMT**
  - $R = H$; Psilocin
  - $R = PO_3H$; Psilocybin

- **5-Methoxy-DMT**

- **Serotonin; 5-HT**

- **LSD**

- **Mescaline**

*Nichols, 2004*
Hallucinogen Effects

- Somatic Symptoms
  - Dizziness, weakness, tremors, nausea, drowsiness, paresthesias and blurred vision
- Perceptual Symptoms
  - Altered shapes and colors, difficulty in focusing on objects, sharpened sense of hearing, synesthesias (joined perception; rare)
Hallucinogen Psychic Effects

- Alterations in mood (happy, sad, irritable),
- Tension and anxiety,
- Distorted time sense,
- Difficulty in expressing thoughts,
- Depersonalization,
- Dreamlike feeling and
- Visual hallucinations or illusions

Hollister 1984
LSD use and kids

Use in Last 12 Months

Perceived Risk

Disapproval

Availability

2009 Monitoring the Future
Lifetime Use of Hallucinogens - 
~25% of people have tried them

Data from US 2004 Monitoring the Future survey, Johnston et al., 2005
LSD
Lysergic acid dimethylamide-25
(LSD$_{25}$)

- Discovered by Albert Hoffman in 1938
- First tried by Hoffman on Friday, April 16, 1943. He rides his bike home and sees an
  - “uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors.”
- First intentional use on Monday, April 19, 1943
- One of the most potent mind altering chemicals known
Albert Hoffman (discoverer of LSD) at his 100th Birthday Party

Photo courtesy of Paul Daley
Ann and Sasha Shulgin at Albert Hoffman’s 100th Birthday Party

Photo courtesy of Paul Daley
LSD Pharmacology

- Dose - 60-200 µg PO
- Duration - 8-12 hours
- Addiction liability - low to none
- Deaths - no human
  - But Tusko the Elephant killed by 297 mg dose injected via dart gun. Mechanism - status epilepticus. Suggests LD$_{50}$ of ~0.06 mg/kg

*West, Science 1962 1100-1103*
Hallucinogens (5-HT$_{2A}$ agonists) dramatically alter consciousness, causing something like a psychosis.

Why?
Hallucinogens (5-HT_{2A} agonists) dramatically alter corticostriato-thalamocortical functioning, causing something like a psychosis.

Why?
Administration of a $5\text{-HT}_{2A}$ Agonist $\rightarrow$
Frontal glutamate release $\rightarrow$
Less thalamic gating $\rightarrow$
Excessive processing of exteroceptive and interoceptive stimuli $\rightarrow$
Collapse of integrative cortical functions.

Vollenweider & Geyer 2001
Serotonergic hallucinogens are 5-HT$_{2A}$ agonists.

5-HT$_{2A}$ receptors are highly expressed on pyramidal cells.

5-HT$_{2A}$ stimulation particularly affects layer V pyramids, some of which provide driving output to subcortical structures.

Hallucinogens cause late asynchronous EPSCs in cortical pyramidal cells, a phenomenon resembling 'up' states.

Lambe and Aghajanian suggest phasic glutamate spillover (cross-talk) from adjacent neurons could explain this & many hallucinogen symptoms.
- $5\text{-HT}_{2A}$ receptors also found to control gain on L5 pyramidal cells.
- Within the neuron, $5\text{HT}_{2A}$ receptors can independently stimulate phospholipase A$_2$, C, and D pathways. The first two don't seem to be 'the' trippy pathways.
- $5\text{-HT}_{2A}$ agonists decrease backpropagation via a phospholipase C pathway.

*Carr et al. 2002; Kurrasch-Orbaugh et al. 2003; Zhang and Arsenault 2005*
It’s worth noting that basic neuroscience studies on $5$-HT$_{2A}$ receptors outnumber those explicitly investigating hallucinogens by a factor of 10!

Recent research on *Salvia Divinorum* and kappa opioid agonists is missing.

Modeling of hallucinogen-induced visuals is missing.
Hallucinogen Persisting Perception Disorder (HPPD)

- The re-experiencing, following cessation of use of a hallucinogen, of perceptual symptom(s) experienced while intoxicated with the hallucinogen
- The symptoms cause clinically significant distress or impairment
- The symptoms are not due to a general medical condition or other disorder.
Pilot Study of Flashbacks:
Symptoms reported by 2.2% (24 of 1090) of respondents who considered treatment

**Description**

56% Stationary objects appear to move or breathe.

56% Repeating patterns (seen with open eyes) such as fields of stars, dots, geometric shapes, etc.

44% Halos or auras around things.

32% Blurry trails or moving objects leave smears or tails in their wake.

28% Perseveration: Complex visions, seen with open eyes, of something that you had just looked at, such as in turning away from an object but still seeing one or more copies of it.

20% Colors increase in brightness or intensity.

20% Things seem to get closer or move further away.

*Baggott, 2010 in press*
Larger Study of Chronic Flashbacks

- 3139 completed a web questionnaire on visual experiences (19.4% out of 16,192 who viewed the information sheet).
- 2678 (85.3%) met inclusion criteria.
- 1652 (61.7%) reported visual experiences reminiscent of hallucinogen effects while not intoxicated.

Baggott, 2010, in press
107 (4%) reported both that symptoms prompted thoughts of treatment and that they lacked diagnoses known to produce unusual visual experiences.

Only 27 had actually sought treatment.

51 (48%) believed a specific episode triggered their symptoms and reported using (in the week before onset):
- cannabis (56.9% of these 51),
- LSD (25.5%),
- psilocybin (23.5%),
- high dose dextromethorphan, (19.6%) and
- MDMA (15.7%).

Baggott, 2010, in press
Recent work with Psilocybin

Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance

R. R. Griffiths • W. A. Richards • U. McCann • R. Jesse
Psilocybin pharmacology

- Psychoactive, naturally occurring tryptamine from *Psilocybe* mushrooms
  - More than 180 species contain psilocybin
  - They grow wild and are easy to cultivate
- Active at $5\text{-HT}_2A/C$ receptors
- Dose: 1-5 grams of dried mushrooms orally
- Duration: 4-6 hours plus additional 2-6 hours of insomnia
- Adverse effects: Nausea, vomiting, anxiety, may interact with MAO inhibitors
Johns Hopkins study

- 30 hallucinogen-naïve volunteers
- All regular participants in religious or spiritual activities
- Drugs and doses:
  - Psilocybin 30 mg / 70 kg
  - Methylphenidate 40 mg / 70 kg
- Three 8-hour sessions separated by 2 months
  - During sessions volunteers instructed to close eyes and direct attention inwards
Immediate ratings of the experience

- Mysticism scale (32 items) of Hood
  - Interpretation
    - Noetic quality, deeply felt positive mood and sacredness
  - Introvertive Mysticism
    - Internal unity, transcendence of time and space and ineffability
  - Extrovertive mysticism
    - Unity of all things/all things are alive
- Also followed HR, BP, Hallucinogen rating scale, APZ, ARCI, States of consciousness questionnaire
Community observer ratings of changes in participants' behavior and attitudes. 3 adult friends of participants rated changes in:

- Inner peace, patience, good natured humor/playfullness, mental flexibility, optimism, anxiety, interpersonal perceptiveness and caring, negative expression of anger, compassion/social concern, expression of positive emotions (joy, love, appreciation) and self-confidence.

Persisting effects questionnaire:

- Mysticism Scale-Lifetime
- Spiritual Transcendence Scale
- NEO Personality Inventory
- PANAS-X
Psilocybin Increased

- **During sessions**
  - Physical contact with monitor (handholding: 72 vs 51 minutes)
  - Anxiety and fear
  - But decreased talkativeness
- **2 months later there were more positive**
  - Attitudes about life
  - Mood changes
  - Altruistic social effects
  - Behavior changes
Psilocybin physiology

- Systolic Blood Pressure
  - Psilocybin (○)
  - Methylphenidate (△)

- Diastolic Blood Pressure
  - Psilocybin (○)
  - Methylphenidate (△)

Timelines: 0, 30, 60, 90, 120, 180, 240, 300, 360 minutes.
67% rated Psilocybin to be either the single most meaningful experience or among the top 5 most meaningful lifetime experiences
- 33% rated Psilocybin as the single most spiritually significant lifetime experience
- An additional 38% rated it in the top 5 most spiritual experiences
- Rated as similar to the birth of a first child or death of a parent
Personal Meaning of the experience rated at 2 months
Ayahuasca is a hallucinogenic botanical brew containing DMT and MAO inhibitors. It is used ceremonially in the Amazon and by several contemporary religions.
An Alphabet Soup of Unstudied Hallucinogenic ‘Research Chemicals’
Studies of potential clinical uses for hallucinogens:
- Anxiety in terminal cancer patients
- Obsessive compulsive disorder
- Cluster headaches (planned)

Increasing basic science studies in Humans:
- Effects on binocular rivalry, time perception, and other psychophysics and neuroscience paradigms
What’s New and Hot? Salvia Divinorum
What is Salvia Divinorum

- Psychoactive plant that is sold over the Internet
- Currently legal and not scheduled by the DEA
Where did it come from

- Mint relative traditionally used for divination and healing in Mazatec zone of Mexico
- Obtained by Wasson and Hoffman from the shaman Maria Sabina in 1955
Abuse Potential

- Considered to be an obscure hallucinogen with little potential for widespread use or abuse.
Usually administered as a extremely bitter infusion prepared from 40 to 160 fresh leaves

Bitterness and number of leaves thought to discourage “all but the most intrepid users”

- Valdes, 1994
Recent Salvia Photo

- Salvia Divinorum plant in bloom
- Photo taken in the wild in the Mazatec region of Mexico

Photo by Cerro Camaron in Seibert, Annals of Botany 93: 776-771 2004
Salvinorin A is...

- ... the active ingredient of Salvia Divinorum
- ... a neoclerodane diterpenoid
- ... the first known nonnitrogenous botanically-occurring kappa opiate agonist

Roth et al. 2002
Salvia Structure

Salvinorin A (C_{23}H_{28}O_{8})
Image by Erowid, © 2002 Erowid.org
Salvinorins A-F, Divinatorins A-C and (-)-Hardwickiic acid

Panel A
- A model of the interactions of Salvinorin A (in blue) with the kappa opioid receptor (KOR, in purple)

Panel B
- A close up view of residues on the KOR that might interact with Salvinorin A

Almost nothing known about Salvia users
Studies of kappa opiate agonists limited by hallucinogen-like effects
Salvinorin-A is a kappa agonist that people like to take - users provide a population to study effects of repeated exposure to kappa agonists
Methods

- 45 question web based survey
  - Both multiple choice and open ended questions
- Recruitment was from Salvia-related pages on Erowid.org, a drug information website receiving 28,000 unique visitors per day
- 500 subjects targeted for enrollment
- Study approved by CPMC IRB
Inclusion and Exclusion

- Included if
  - Prior use of Salvia

- Excluded for
  - Living in Australia, incomplete responses, previous submission of survey, submission of survey from same computer within 10 minutes, not fluent in English, no prior Salvia use

- Could not verify age, so age not used to exclude
How long did it take?

- The study information sheet and questionnaire was viewed 1298 times, with 520 (40.1%) submitting a completed questionnaire.
- 500 of 520 (96.2%) responses met inclusion/exclusion criteria.
- Took about 2 weeks.
463 (92.6%) were male, 37 were female
Age was 23.4 ± 8.7; range 13 – 68 years old; 20.2% were minors (under 18)
77.4% reported living in the United States
80.6% probably or definitely would use Salvia again
# Number of Salvia exposures

<table>
<thead>
<tr>
<th>Use In the…</th>
<th>X±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>last 30 days</td>
<td>1.5±2.6</td>
<td>0-24</td>
</tr>
<tr>
<td>last year</td>
<td>7.5±1.2</td>
<td>0-110</td>
</tr>
<tr>
<td>ever</td>
<td>13±23</td>
<td>1-250</td>
</tr>
</tbody>
</table>
Most (92.6%) typically smoked or vaporized Salvia product
- 61.4% used a concentrated extract
- 37.3% used dried leaf
- 4.2% had used purified salvinorin A
- Salvia was often used in darkness (62.2%), with music (44.6%), or with a sober companion (38.6%)
# Estimated Duration of Effects when Smoked (in minutes)

<table>
<thead>
<tr>
<th>Form</th>
<th>X±SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD extract (N = 296)</td>
<td>14.1±12.8</td>
<td>0.5</td>
<td>120</td>
</tr>
<tr>
<td>SD leaf (N = 180)</td>
<td>16.2±14.8</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>Salvinorin A (N = 6)</td>
<td>27.5±16.1</td>
<td>13</td>
<td>50</td>
</tr>
</tbody>
</table>
Salvia effects - compared to other methods of altering consciousness

- 38.4% reported Salvia is unique
- 23.2% reported Salvia is like meditation/yoga/trances
- 17.7% reported Salvia is like serotonergic hallucinogens (e.g. LSD)
- 7.1% reported Salvia is like dreaming
- 6.8% reported Salvia is like NMDA antagonists (e.g. Ketamine) and other anesthetics
- 6.5% reported Salvia is like Cannabis
25.8% reported persisting (24 hrs or more) positive effects (most often increased sense of well-being) on at least one occasion.
4.4% reported persisting (>24 hrs) negative effects (most often anxiety) at least once.
- 0.6% had sought professional help for a Salvia-related problem on at least one occasion.
- One went to a priest to discuss Catholicism.
- A polydrug abuser (DMT, dextromethorphan, Salvia, methamphetamine, diphenhydramine, “etc.”) sought emergency psychiatric care for what may have been stimulant psychosis.
- One respondent visited a psychologist or a psychotherapist.
3 (0.6%) felt addicted to or dependent upon Salvia at some point
6 (1.2%) reported strong cravings for SD at some point
2 (0.4%) endorsed three DSM-IV dependence criteria at some point.
None of these individuals endorsed more than 2 of 13 after-effects characteristic of µ-opiate withdrawal
Lingering Effects after Intoxication

- 47% reported increased insight
- 44.8% reported improved mood
- 42.2% reported calmness
- 39.8% reported increased connection with the universe or nature
- 36.4% reported weird thoughts
Most respondents smoke/vaporize Salvia products, in contrast to traditional Mazatec method of oral ingestion.

Serious adverse events are rare in this young and computer literate population, although the toxicity of new drugs is often only detected as use spreads.

Dependence appears rare in this population, although animal studies suggest kappa agonist can induce a withdrawal syndrome comparable to μ-agonists.
What did we skip

- But may still be on the exam:
  - GHB
  - MDA
  - PCP
- Thanks for your attention.
The Talent - Our Underpaid Staff

- Co Investigators
  - Gantt Galloway, Mathew Baggott, Keith Flower

- Professional Staff
  - Michelle Salinardi, Our Boss
  - Raymond Buscemi, Jeremy Coyle, Tuli Cruz, Ekatrina Dib, Laurel Fiske, Kathleen Garrison, Sasha Gruzdeva, Jose Guillen, Will Harris, Danielle Hubbard, Margie Jang, Linghui Li, Jayme Mulkey, Emma Olson, Jennifer Siegrist

- Support for these studies - DA 18179, DA 16776, DA 17716
Questions?