Stimulants: Cocaine and Methamphetamine

CRIT program - May 2012

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Assistant Professor of Medicine
Learning objectives

At the end of this session, participants will be able to:

1. Understand how and why people use stimulants
2. Know the characteristics of stimulant intoxication and withdrawal syndromes
3. Understand the consequences of these drugs
4. Know the current options for treatment of stimulant dependence
Roadmap

1. History
2. Epidemiology
3. Dopamine and the reward pathway
4. Acute and chronic effects
5. Treatment
History: Cocaine

- From erythroxylon coca leaves in Andes
- Leaves chewed for thousands of years as stimulant
- 1884 Freud published, *Uber Coca*, describing cocaine’s effects on Freud and its potential to treat opiate addiction
- 1885 Halsted published study about anesthetic uses
- 1886 Halsted raided ship medicine cabinet for fix
- Used in medicines and beverages until early 1900s
- Street preparations 10-50% cocaine
  - Hydrochloride powder is snorted or injected
  - Alkaline rocks (aka crack) are smoked
  - *Crack, Rock, Base*
History: Methamphetamine

- 1893 methamphetamine first synthesized in Japan as decongestant.
- Used by German, English, American, and Japanese military in WWII for performance enhancement.
- First epidemic occurred in Japan when the military dumped large quantities into the civilian market.
- Popular among truckers and west coast bikers in 1970s.
- DESOXYN to treat ADHD and obesity.
- *Speed, Crystal, Crank, Ice, Meth, Tina*
Epidemiology
Past Month Use: 2002-2008

CRIT 2012  NSDUH 2008
2005 drug-related ED visits

Drug Abuse Warning Network 2005 Report

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Percent Male Arrestees Testing Positive for Meth (for 33 ADAM sites, 2001)
From where do these drugs come?

• Methamphetamine
  – Super labs – Primarily Mexico and California
  – Local clandestine labs - 1 pound of MA creates 6 pounds of toxic waste

• Cocaine -
  – 75% grown in Columbia with 75% via Mexico/ Central America
Cocaine processing

http://www.colombiajournal.org/cocainephotos.htm
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Clandestine lab incidents

Total of All Meth Clandestine Laboratory Incidents
Including Labs, Dumpsites, Chem/Glass/Equipment
Calendar Year 2004

Source: National Clandestine Laboratory Database
Total: 15,994 / 49 States Reporting
Dates: 01/01/04 to 12/31/04

Total of All Meth Clandestine Laboratory Incidents
Including Labs, Dumpsites, Chem/Glass/Equipment
Calendar Year 2006

Source: National Clandestine Laboratory Database
Total: 6,435
Dates: 01/01/2006 - 12/31/2006

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Stimulant Effects
Why do people use drugs?

1. To feel good
2. To feel better
Why do people use stimulants?

• Euphoria - Rush
  – Onset and intensity depends on delivery method
• Increased energy, alertness, libido
• Diminished social inhibition
• Decreased appetite

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Cocaine

Methamphetamine

Transmitting Neuron

Dopamine packaged in vesicles

Dopamine transporter functioning normally

Dopamine transporter blocked by cocaine

Cocaine

Receiving Neuron

Dopamine Receptors

Methamphetamine stimulates the release of excess dopamine.
Which statement is true about stimulants?
A. Methamphetamine is only used intravenously or smoked
B. Methamphetamine has a longer half-life than cocaine
C. Intravenous injection results in the fastest onset of action
D. Cocaine’s peak concentration occurs in about 1 hour
### PK: Cocaine

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>Smoked</th>
<th>Snorted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to effect</td>
<td>10-60sec</td>
<td>3-5sec</td>
<td>1-5min</td>
</tr>
<tr>
<td>Peak concentr.</td>
<td>3-5min</td>
<td>1-3min</td>
<td>15-20min</td>
</tr>
<tr>
<td>Half-life</td>
<td>20-60min</td>
<td>5-15min</td>
<td>60-90min</td>
</tr>
</tbody>
</table>


### PK: Methamphetamine

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>Smoked</th>
<th>Snorted</th>
<th>Ingested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to effect</td>
<td>15-30 sec</td>
<td>Immediate</td>
<td>3-5 min</td>
<td>15-20 min</td>
</tr>
<tr>
<td>Peak concentr.</td>
<td>2-4 h</td>
<td>2-4 h</td>
<td>2-4 h</td>
<td>2-4 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>10-12 h</td>
<td>10-12 h</td>
<td>10-12 h</td>
<td>10-12 h</td>
</tr>
</tbody>
</table>

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Lineberry 2006
Binges

• 2-3 day binges are typical, called runs
• Regular re-dosing to maintain rush or high in setting of acute tolerance
• Ends when drug or money runs out, or paranoia/ disorganized thinking sets in
Acute Toxicity

- Elevated BP and HR
- Arrhythmia
- Vasoconstriction
- Hyperthermia
- Acute psychosis → prolonged psychosis
  - Paranoid delusions
  - Visual, sensory, and auditory hallucinations (ie formications)
- Agitation
- Rhabdomyolysis
- Seizure

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Intoxication Treatment

- Minimize sensory stimulation
- Neuroleptics (ie haldol) for agitation
- Benzos to control seizures
- Treat hyperthermia (external cooling)
- For increased BP+HR, use vasodilators and CCB or non-selective beta-blockers
Is there stimulant withdrawal?

• Intense craving
• Depression
• Fatigue
• Unpleasant dreams
• Hypersomnia, then insomnia
• Increased appetite
• Limited ability to experience pleasure

>> All results of relative dopamine depletion
Health Consequences
Dental
- Darkened teeth
- Caries
- Periodontal disease

Pulmonary
- Acute pulmonary edema
- Pulmonary HTN
- Inhalation injury

Cardiovascular
- Hypertension
- DCM
- Arrhythmia/ Tachycardia
- Acute Coronary Syndrome
- Aneurysm/ dissection
- Erectile dysfunction

Infectious
- HIV risk
- HCV/ HBV
- STDs

Neuro-psychiatric
- Stroke
- Seizure
- Depression
- Anxiety
- Mania
- Impulsivity
- Paranoia
- Auditory/ visual hallucinations + formications
- Violence

Renal/Metabolic
- Rhabdomyolisis
- Dehydration
- Acute Renal Failure
- Acidosis
- Hyperthermia

Skin
- Cellulitis/ abscess
- Excoriations
- Chemical burns
AHA 2008 Scientific Statement on cocaine chest pain and MI

• Class I: Benefit >>> Risk
  – Benzodiazepines (Level B)
  – ASA (Level C)
  – NTG (Level B)

• Class IIb: Benefit ≥ Risk
  – CCB (Level C)
  – Phentolamine (Level C)

• Class III: Risk ≥ Benefit
  – Beta-blockers (Level C)

Audience Response II

Studies of the treatment for cocaine-related unstable angina with beta-blockers

A. include randomized controlled trials that demonstrate that they save lives
B. include randomized controlled trials that demonstrate that they cause harm
C. include catheter studies in humans that show worsening vasospasm with propanolol
D. include observational studies that show no increased adverse events among people receiving beta-blockers in the ED
Beta-Blockers in Cocaine Chest Pain

331 patients with chest pain and cocaine-positive urine test results admitted to San Francisco General Hospital between 2001-05

• 151 patients received a beta-blocker in ED
  – 85% received metoprolol

• During the hospitalization
  – SBP decreased more in ED beta-block group
  – No differences in ECG results, troponin levels, intubation rates, vasopressor use, malignant ventricular arrhythmia rates, or death were found.

• 45 deaths over a median follow-up of 972 days
  – Discharge on a beta-blocker regimen was associated with a lower risk of cardiovascular-specific death but not all-cause mortality


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Cocaethylene

- Psychoactive substrate from EtOH+cocaine
- ETOH commonly used as “landing gear”
- ETOH before cocaine inhibits cocaine metabolism, producing cocaethylene
- 60-90% of cocaine abusers abuse ETOH
- Greater cardiac toxicity
- Greater rates of seizures, hepatic damage

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Cocaine and heroin

- 30-80% of heroin users use cocaine
- Cocaine use results in more injections
- Cocaine worsens opiate treatment success
- For 50% of co-users, MMT reduces cocaine
Treatment
Pharmacologic Treatment

• **Antipsychotics**

• **Anticonvulsants - GABA modulators**

• **Stimulant replacement**

• **Vaccine**

Non-Pharma Treatment

• Brief Intervention?
  – Bernstein et al. DAD 2005; 77: 49.

• Cognitive behavioral therapy

• Self-help/ 12 step groups

• Residential Treatment

• Contingency management
Contingency Management

RCT in 6 community methadone programs of CM among stimulant users

• Usual Care vs.
• Intermittent, escalating re-enforcement
  – 1000 chips
    • 500 “Good job”
    • 250 “Small” - $1 value – i.e. toiletries
    • 209 “Large” - $20 value – i.e. kitchenware
    • 1 “Jumbo” – $80-100 value – tv, stereo
  – # of draws = # of weeks with clean urine

The mean percentage of submitted samples testing negative for target drugs (stimulants and alcohol) is shown for abstinence incentive and usual care participants at each of 24 study visits.
Contingency Management

Methadone Maintenance Patients With Specified Weeks of Continuous Stimulant/Alcohol-Negative Samples (n=388)

Average cost = $1.46 per person/day

Pierce et al. Arch Gen Psychiatry. 2006;63:201-208.
What should we do with our stimulant-using patients?

• For both inpatients and outpatients
  – Ask about overdose, medical complications
  – Harm reduction – safer use techniques
  – Motivational interviewing to develop a decisional balance that favors safer use, quitting and engaging in available treatment

• Consider contingency management strategies
Thanks!

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2007 ACC/AHA guidelines
UA/ NSTEMI in cocaine and methamphetamine

- Class I: Benefit >>> Risk
  - For STE or STD: NTG and CCB
  - For persistent STE: Cath with PCI or lytics
- Class IIa: Benefit > Risk
  - Chest pain w/o ST changes: NTG and CCBs
  - STD or new TW changes: Cath
- Class IIb: Benefit ≥ Risk
  - Increased HR or BP: Mixed alpha/beta blocker after vasodilator
- Class III: Risk ≥ Benefit
  - No ST changes: Cath

Note: Level of evidence is C “expert opinion” for all recommendations

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Pharmacologic Treatment

- Pharmacologic treatments studied
  - Dopamine agonists
  - Antidepressants
  - Opioid partial agonists and antagonist
  - Carbamazepine, phenytoin, lithium

- None proven effective


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5 things about stimulants

1. Easily available
2. Directly activate the mesolimbic pleasure center
3. Binge use often ends with dysphoria or lack of funds
4. Social and medical consequences
5. Treatment can work if you can find it
Learning objectives

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Dopamine release: nucleus accumbens

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Increased myocardial oxygen demand with limited oxygen supply

Increased heart rate
Increased blood pressure
Increased myocardial contractility

Vasoconstriction

Increased α-adrenergic stimulation
Increased endothelin production
Decreased nitric oxide production

Accelerated atherosclerosis and thrombosis

Increased plasminogen-activator inhibitor
Increased platelet activation and aggregability
Increased endothelial permeability
Natural Rewards Elevate Dopamine Levels

**FOOD**

NAc shell

- % of Basal DA Output
- Time (min)

- Empty
- Box
- Feeding

**SEX**

- DA Concentration (% Baseline)
- Copulation Frequency

- Sample Number
- Female 1 Present
- Female 2 Present

Source: Di Chiara et al.

Source: Fiorino and Phillips

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Slide from Richard Rawson
Effects of Drugs on Dopamine Release

- **METHAMPHETAMINE**
  - Graph showing time after methamphetamine and % of basal release.

- **COCaine**
  - Graph showing time after cocaine and % of basal release.

- **NICOTINE**
  - Graph showing time after nicotine and % of basal release.

- **ETHANOL**
  - Graph showing time after ethanol and % of basal release.

Source: Shoblock and Sullivan; Di Chiara and Imperato

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According to the Drug Enforcement Agency (DEA), crystal methamphetamine (meth) is the number one drug in rural America. And now, the crystal meth epidemic is spreading like wildfire in cities and suburbs across America. Crystal meth has become the new drug of choice for everyone from soccer moms to working moms. Even grade school students are being caught in its deadly grip.

Meth is cheap and easy to make. The recipe includes over-the-counter cold medicine, household cleaners and toxic chemicals like battery acid. This drug crisis has forced many store owners to put cold remedies under lock and key. Thousands of homemade meth labs are popping up in kitchens, garages, even inside cars. In one Iowa town officials were forced to ban children from bringing baked goods to school because so many parents are cooking meth with the same utensils.

It's cheap, instantly addictive, often deadly—and it's probably already in your neighborhood.
She says she's been addicted to meth for a year and a half, after being introduced by friends, and she says she was instantly hooked from the very first hit. Since that time, she says the longest she's gone without using meth was 40 days. In that time, Chantel says, "I was having a ball. I was going to church to see if that was the way for me. I was having fun, hanging out with sober people. And then it was just in front of me one night and I did it and I was hooked again."

On one occasion, Chantel says she stayed up for 13 straight days, getting high every 20 minutes. "Meth makes you have this burst of energy," she explains. "And if you keep smoking it, you'll keep that energy burst." Was she worried about overdosing during that two-week binge? "You don't worry about anything," Chantel says. "You don't have any thought in your mind besides, 'Let's hit it again.'"
Pregnancy

• More common in stimulant users:
  – Mental illness, seizure, injury, hypertension
  – Premature membrane rupture and labor, placenta previa, placental abruption, intrauterine death

• 1998-2004
  – Cocaine-related hosp decreased: 0.74>>0.41 per 100
  – MA-related hosp increased: 0.11>>0.22 per 100

• Cocaine vs. MA related pregnancy
  – More common for cocaine: mental illness, poor fetal growth, and premature delivery
  – More common for MA: hypertension, placenta previa

2005 drug-related ED visits

Drug Abuse Warning Network 2005 Report

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Cardiomyopathy and Methamphetamine

In a case-control study, researchers examined the association between methamphetamine use and cardiomyopathy (CM).

Subjects included patients aged 45 years or younger discharged from a tertiary care medical center in Honolulu.

Through medical record review, researchers identified...

- 107 cases (had a discharge diagnosis of CM or congestive heart failure) and
- 114 controls (ejection fraction $\geq 55\%$ and no wall motion abnormalities).

Cardiomyopathy and Methamphetamine

- 42% of cases and 20% of controls had ever used methamphetamine.
- Methamphetamine use was significantly more common in cases than in controls.
- OR in analyses adjusted for age, body mass index, and renal failure, 3.7
“No lies here folks this recipe will manufacture methamphetamine this will get you into trouble if you do this BE CAREFUL!”

First of all let's talk about supplies:

• 1 Case Regular Pint size Mason Jars (Used for canning)
• 2 Boxes Contact 12 hour time released tablets.
• 3 Bottles of Heet.
• 4 feet of surgical tubing.
• 1 Bottle of Rubbing Alcohol.
• 1 Gallon Muriatic Acid (Used for cleaning concrete)
• 1 Gallon of Coleman's Fuel
• 1 Gallon of Aceton
• 1 Pack of Coffee Filters
• 1 Electric Skillet
• 4 Bottles Iodine Tincture 2%
• 2 Bottles of Hydrogen peroxide
• 3 20 oz Coke Bottles (Plastic type)(with Lids/caps)
• 1 Can Red Devils Lye
• 1 Pair of sharp scissors
• 4 Boxes Book Matches (try to get the ones with brown/red striker pads)
• 1 pyrodex baking dish
• 1 Box execto razor blades single sided
• 1 digital scale that reads grams
• 2 gallons distilled water
• 1 Roll Aluminum foil tape

“That's what you would have to go buy if you wanted to make meth.”

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Treating Methamphetamine Dependence Reduces Risk for HIV

Objectives/Methods

• 787 methamphetamine-dependent individuals who received 1 of 2 counseling strategies:
  – 16 weeks of a standardized psychosocial protocol (Matrix Model), or
  – 8–16 weeks of treatment-as-usual representing 8 diverse treatment approaches

• Both approaches focused on drug use, not HIV risk
Results

- The proportion of the sample who reported injecting methamphetamine within the previous 30 days declined significantly (14.6% to 5.4%) from baseline to discharge.

- High-risk sexual activity also decreased:

<table>
<thead>
<tr>
<th>Activity Description</th>
<th>Baseline</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean times participants reported having sex without a condom</td>
<td>14.7</td>
<td>13.2</td>
</tr>
<tr>
<td>Mean times participants reported having sex without a condom with a methamphetamine user</td>
<td>2.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Mean times participants reported having sex without a condom with an injection drug user</td>
<td>6.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Mean times participants reported having sex while high</td>
<td>9.1</td>
<td>4.9</td>
</tr>
</tbody>
</table>

- There were significant associations between treatment retention and HIV risk outcomes.

Results – long term follow-up

![Bar graph showing mean number of risky sex behaviors (past month) at different time points: baseline, tx-end, 6 months, 12 months, and 3 yrs.](Image)

N=569

Comments

- This study demonstrates the benefit of counseling for patients with methamphetamine dependence.

- Treatment was associated with decreased methamphetamine use and decreased risk for HIV infection.

- The association between treatment retention and reduced HIV risk supports the implementation of programs that reduce barriers for treatment entry and retention.
Cocaine and HIV

- Crack cocaine use is associated
  - increased number of sex partners
  - sex work
  - HIV infection, independent of IVD use

- IV cocaine leads to HIV through frequent injection

MA and HIV

• Increased libido, social disinhibition, increased energy >> riskier sex behaviors
• PDE5 inhibitors (sildenafil) can be used to mitigate MA-induced erectile dysfunction
Methamphetamine and Trauma

To assess the prevalence and impact of methamphetamine use (MU) in trauma patients, researchers surveyed the records of…

- 4932 patients who presented to
  - San Diego trauma center between 2003–2005
  - urine toxicology screening during their visit

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Results

• The rate of MU (defined as a positive urine screen), but not other illicit drug use, increased from 2003 to 2005 (from 9% to 15%).

• In adjusted analyses, patients with MU were more likely to have...

  – been injured in a violent way (OR, 2.0),
  – attempted suicide (OR, 1.7),
  – been a victim of domestic violence (OR, 2.5),
  – required more medical care (e.g., ≥1 operations [OR, 1.5], mechanical ventilation [OR, 1.6]), and
  – died from their injuries (OR, 2.3).

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Cognitive Behavioral Therapy

16 week RCT of cocaine-dependent methadone patients of:
   CBT vs. CM vs. CBT+CM vs. TAU
30 patients per group

Rawson et al. Arch Gen Psychiatry. 2002
Cognitive Behavioral Therapy

**Figure 5.** Percentage of patients achieving 3 consecutive weeks of cocaine-free urine samples by group ($\chi^2_3 = 9.9; \ P = .02$). CBT indicates cognitive-behavioral therapy; CM, contingency management; and MMTP, methadone maintenance treatment program.
Cognitive Behavioral Therapy

Figure 6. Percentage of 30 possible cocaine-free urine samples at the 17-week, 26-week, and 52-week follow-up points. CBT indicates cognitive-behavioral therapy; CM, contingency management; and MMTP, methadone maintenance treatment program.