Stimulants: Cocaine and Methamphetamine

CRIT program - May 2012

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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

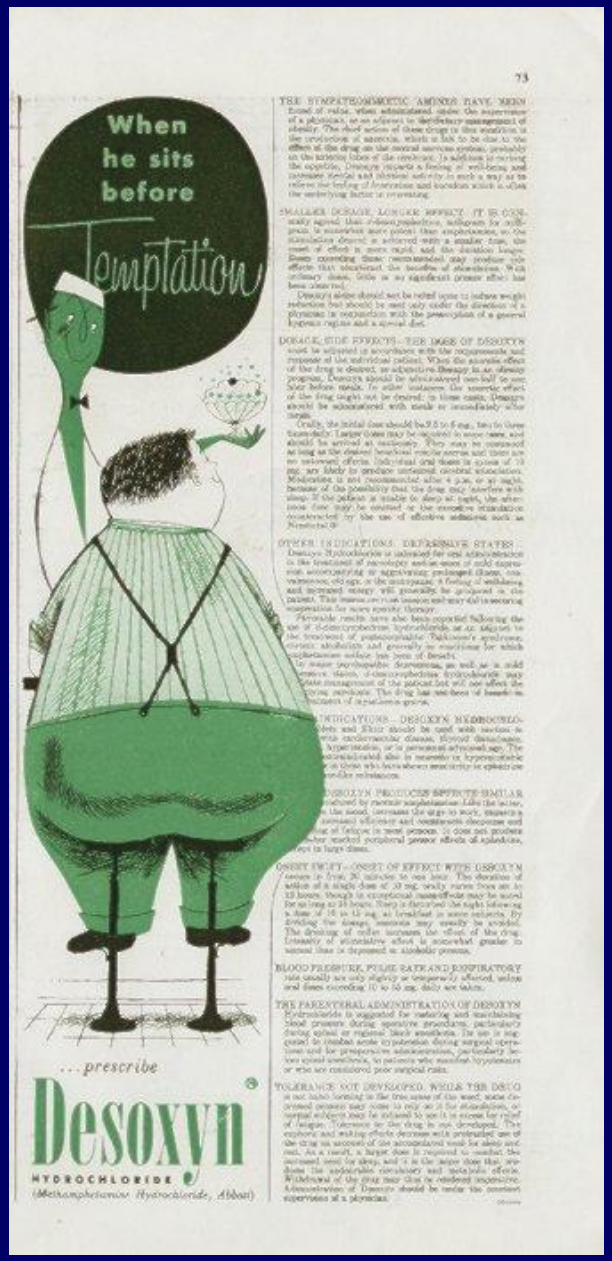
1885 Advertisement for Cocaine Toothache Drops

- 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*

Lineberry 2006



1957

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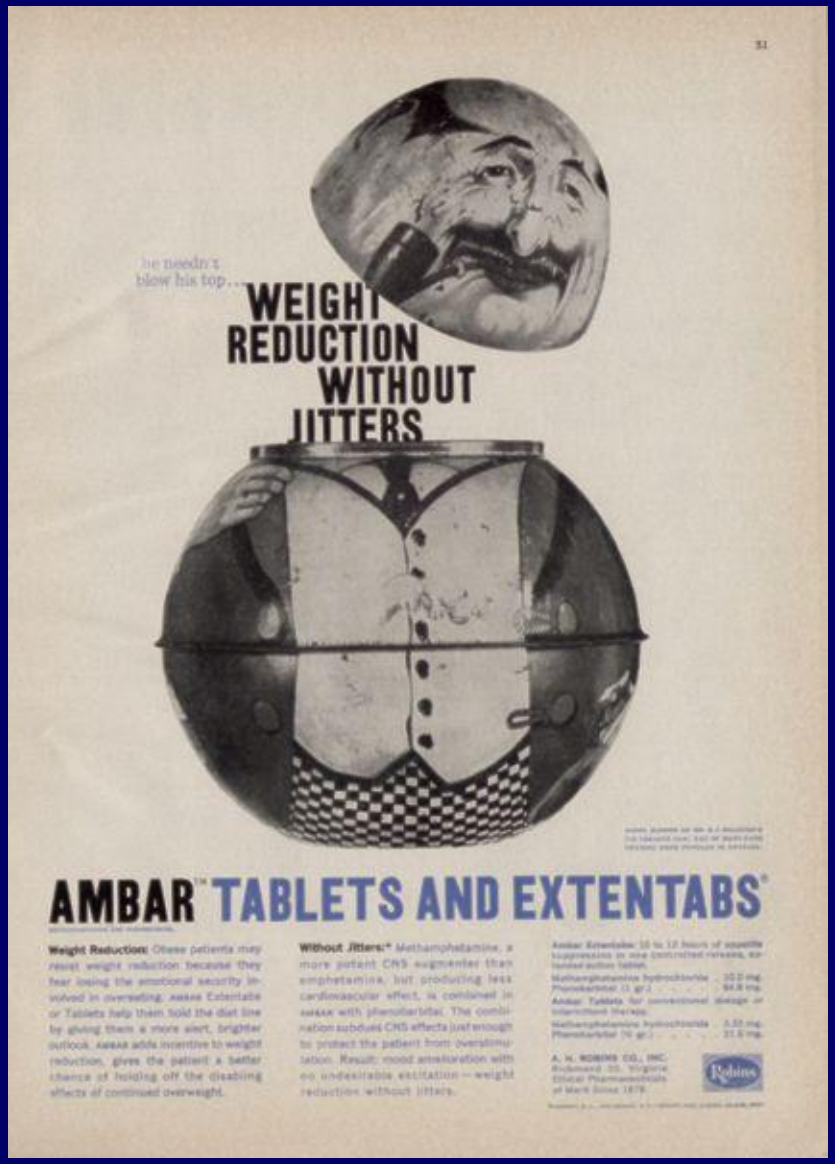
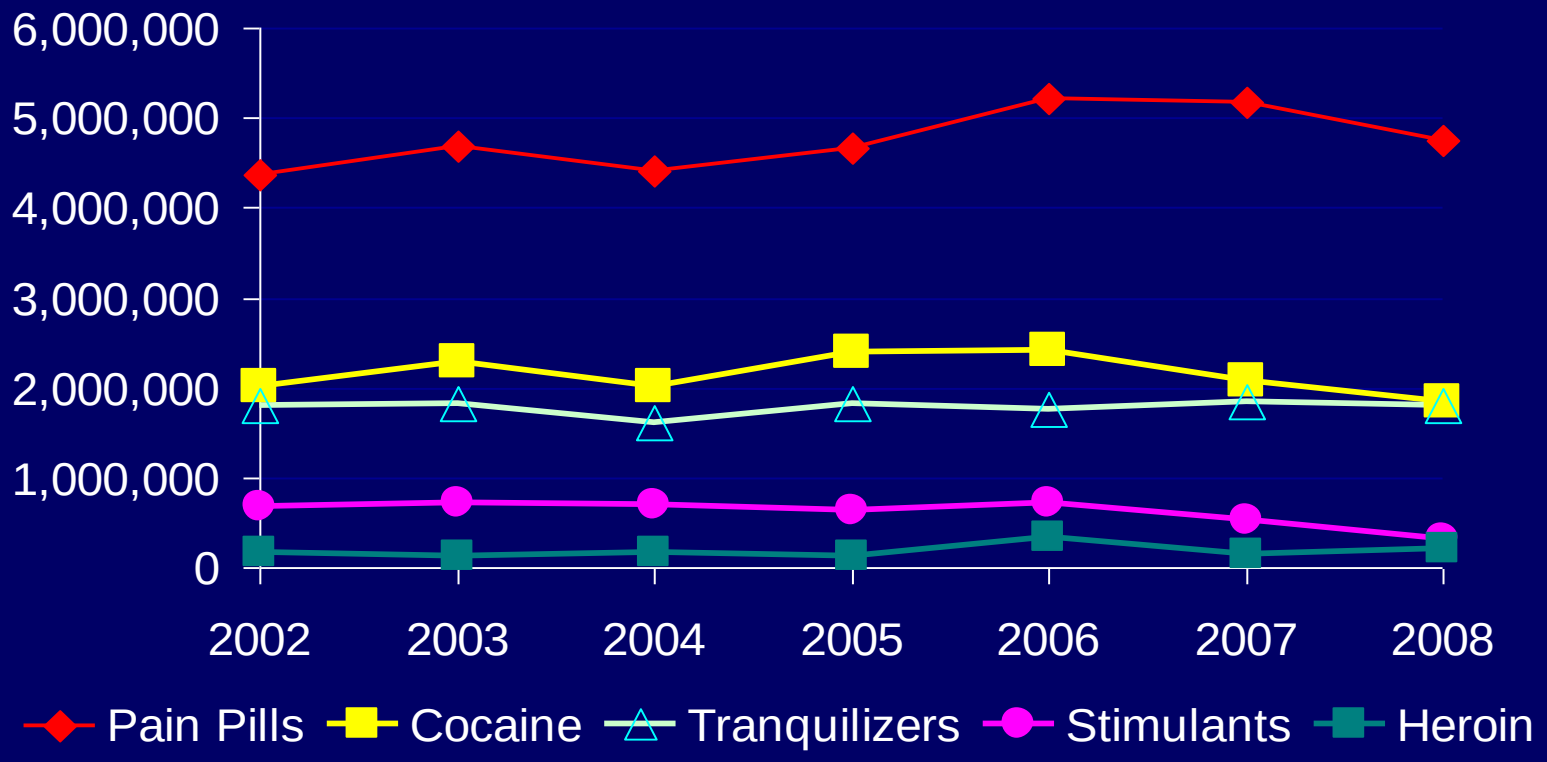


1959

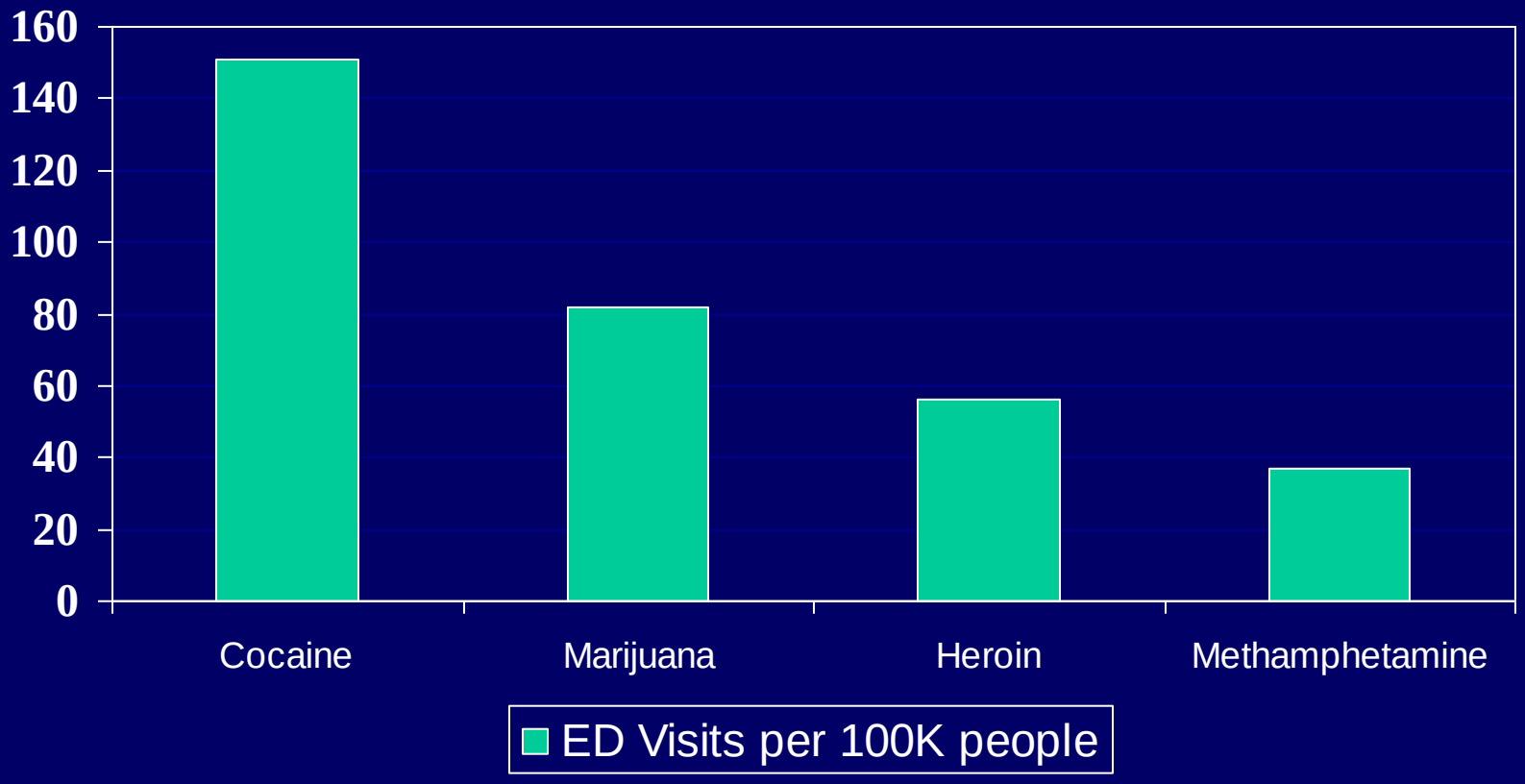
Epidemiology

Past Month Use: 2002-2008



CRIT 2012 NSDUH 2008

2005 drug-related ED visits



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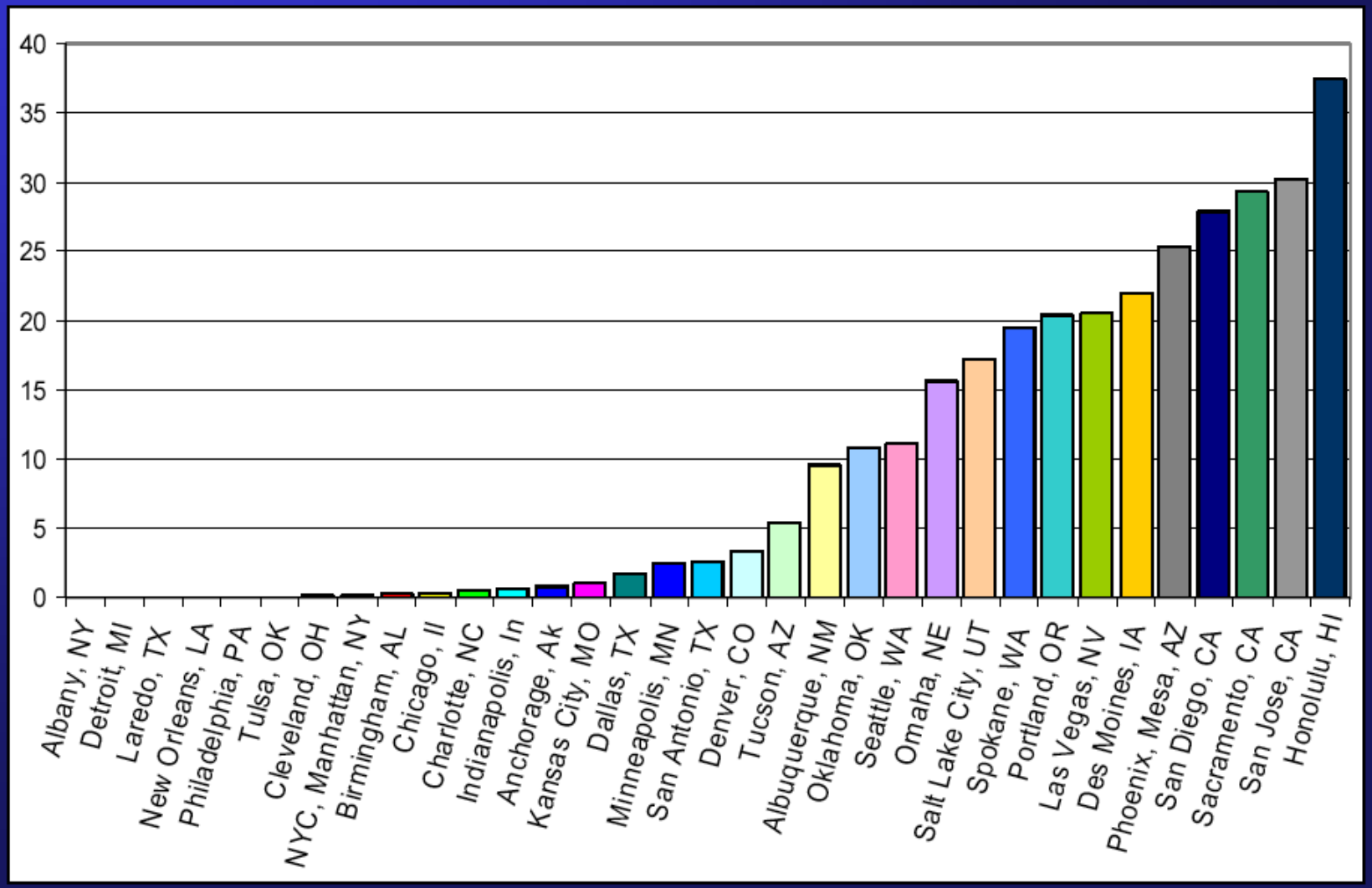
Drug Abuse Warning Network 2005 Report

Percent Male Arrestees Testing Positive for Meth (for 33 ADAM sites, 2001)



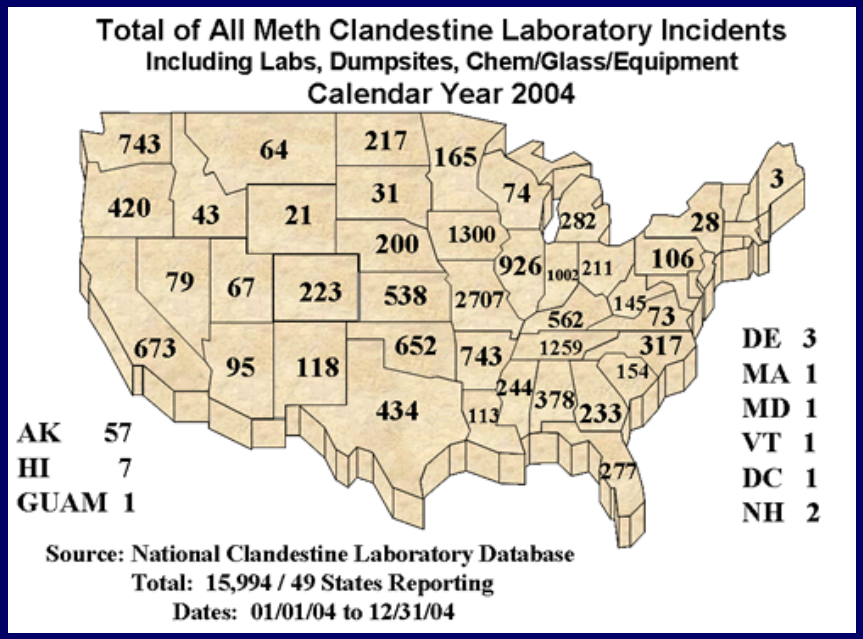
From where do these drugs come?

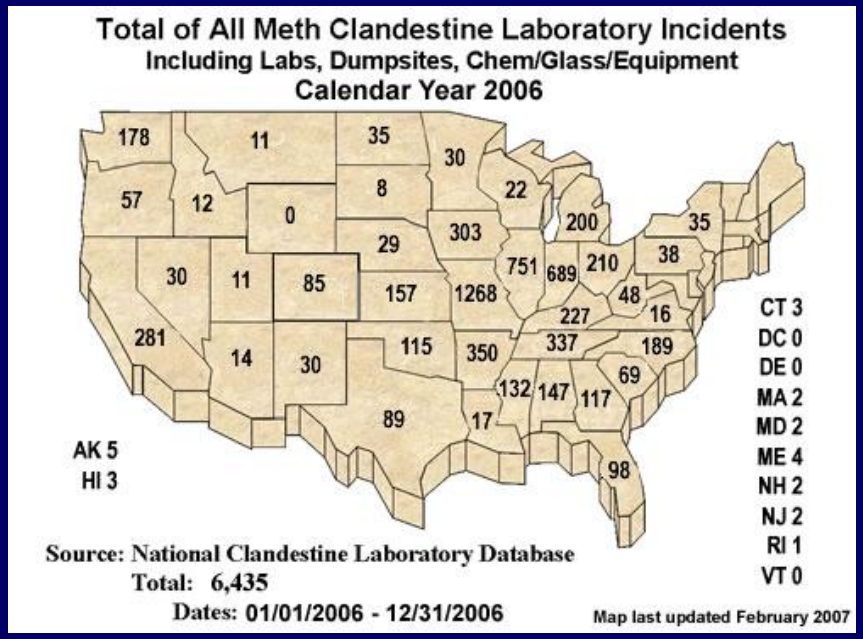
- Methamphetamine
  - Super labs – Primarily Mexico and California
  - Local clandestine labs - 1 pound of MA creates 6 pounds of toxic waste
    - Holton WC. Unlawful lab leftovers. *Environ Health Perspect.* 2001;109:A576
- Cocaine -
  - 75% grown in Columbia with 75% via Mexico/ Central America

Cocaine processing

http://www.colombiajournal.org/cocainephotos.htm

Clandestine lab incidents





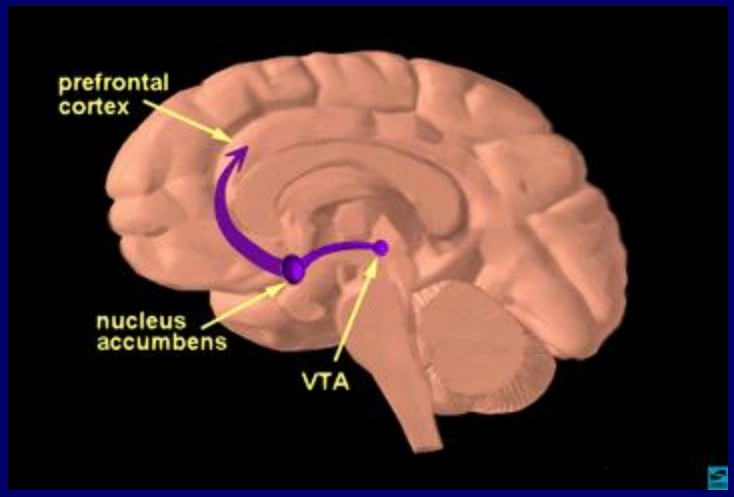
Stimulant Effects

Why do people use drugs?

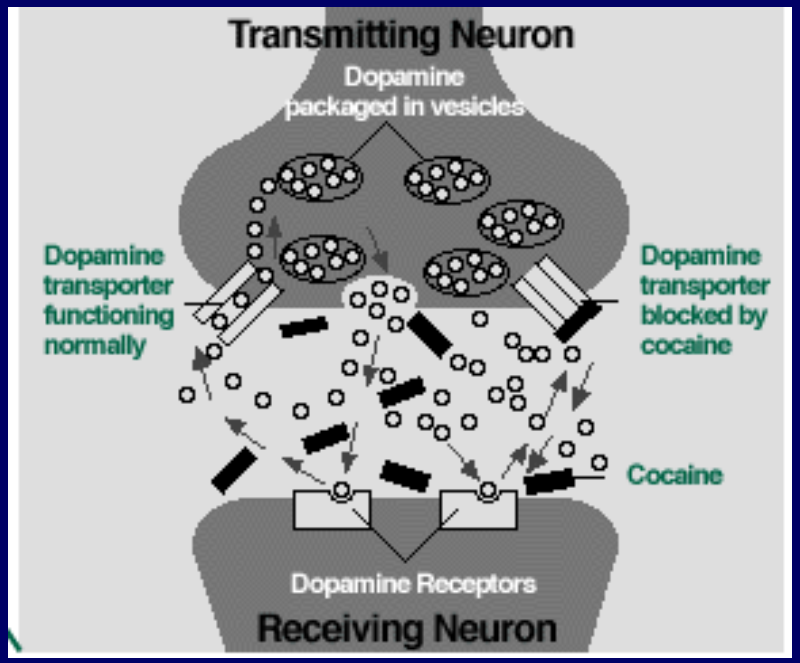
1. To feel good
2. To feel better

Why do people use stimulants?

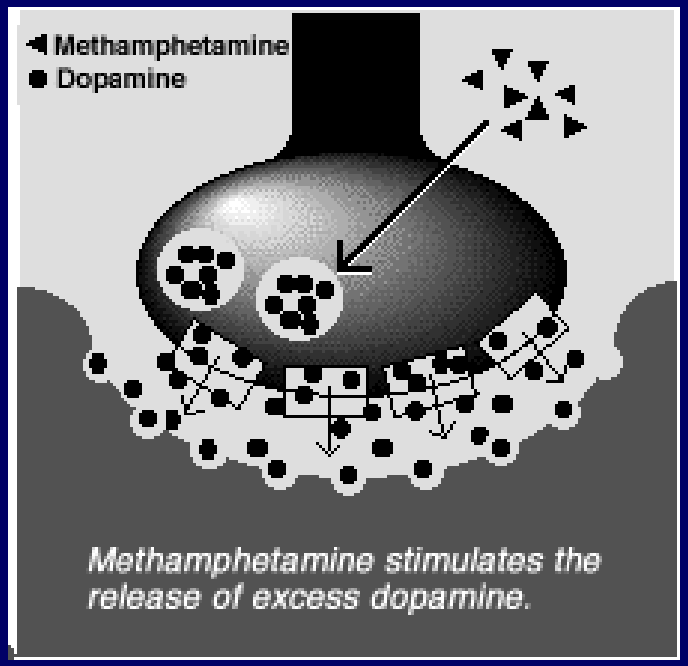
- Euphoria - Rush
  - Onset and intensity depends on delivery method
- Increased energy, alertness, libido
- Diminished social inhibition
- Decreased appetite



Cocaine



Methamphetamine



Audience Response I

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

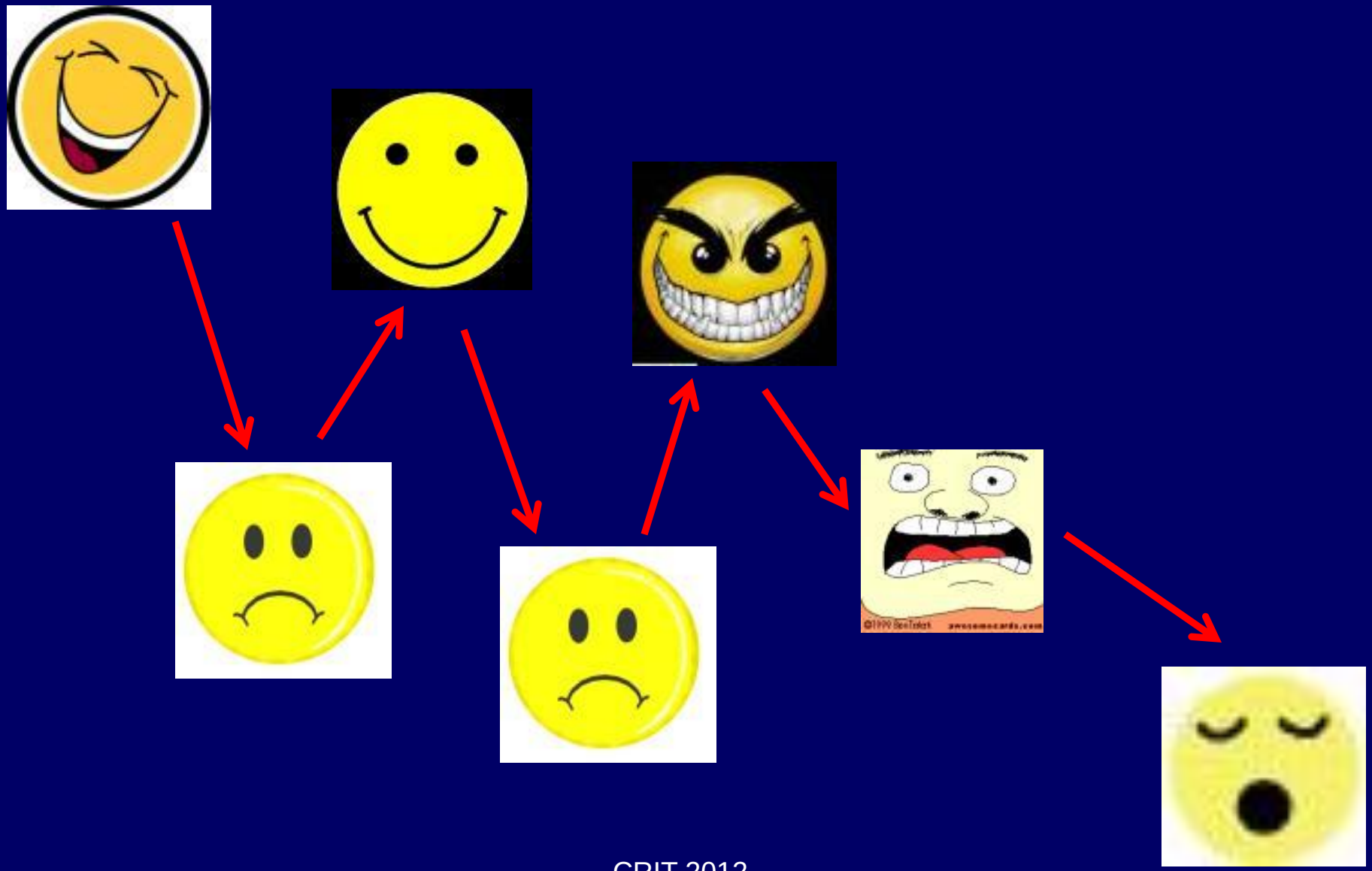
	IV	Smoked	Snorted
Time to effect	10-60sec	3-5sec	1-5min
Peak concent.	3-5min	1-3min	15-20min
Half-life	20-60min	5-15min	60-90min

Lange, R. A. and L. D. Hillis (2001). "Cardiovascular complications of cocaine use." N Engl J Med **345**(5): 351-8.

PK: Methamphetamine

	IV	Smoked	Snorted	Ingested
Time to effect	15-30 sec	Immediate	3-5 min	15-20 min
Peak concent.	2-4 h	2-4 h	2-4 h	2-4 h
Half-life	10-12 h	10-12 h	10-12 h	10-12 h

Lineberry 2006



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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
- Arrythmia
- Vasoconstriction
- Hyperthermia
- Agitation
- Rhabdomyolysis
- Seizure
- Acute psychosis → prolonged psychosis
  - –Paranoid delusions
  - –Visual, sensory, and auditory hallucinations (ie formications)

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
- Arrythmia/ Tachycardia
- Acute Coronary Syndrome
- Aneurysm/ dissection
- Erectile dysfunction

Infectious

- HIV risk
- HCV/ HBV
- STDs

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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)

McCord et al. Circulation. 2008: 117.

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

Rangel C, Shu RG, Lazar LD, et al. Beta-blockers for chest pain associated with recent cocaine use. *Arch Intern Med.* 2010;170(10):874–9.

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

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

Leri F. Addiction 2003: 98, 7-22.

Treatment

Pharmacologic Treatment

- Antipsychotics
  - Amato. Cochr Database Syst Rev. 2007 Jul 18;(3):
- Anticonvulsants - GABA modulators
  - Carbamazepine, Phenytoin, Valproic Acid, Tigabine, Gabapentin, Lamotrigine – Alvarez. JSAT 2010: 38; 66-73.
  - Baclofen – Heinzerling. Drug Alcohol Depend. 2006 Dec 1;85(3):177-84.
  - Vigabatrin (GVG) – Brodie. Am J Psychiatry. 2009;166:1269-77.
- Stimulant replacement
  - Modafinil – Shearer. Addiction. 2009 Feb;104(2):224-33.
  - Dexamphetamine – Longo. Addiction 2009, 105, 146–154
- Vaccine
  - Martell. Arch Gen Psychiatry. 2009 Oct;66(10):1116-23.
- Disulfiram – Pani. Cochr Database Syst Rev. 2010 Jan 20;(1):

Non-Pharma Treatment

- Brief Intervention?
  - Bernstein et al. DAD 2005; 77: 49.
- Cognitive behavioral therapy
- Self-help/ 12 step groups
- Residential Treatment
- Contingency management

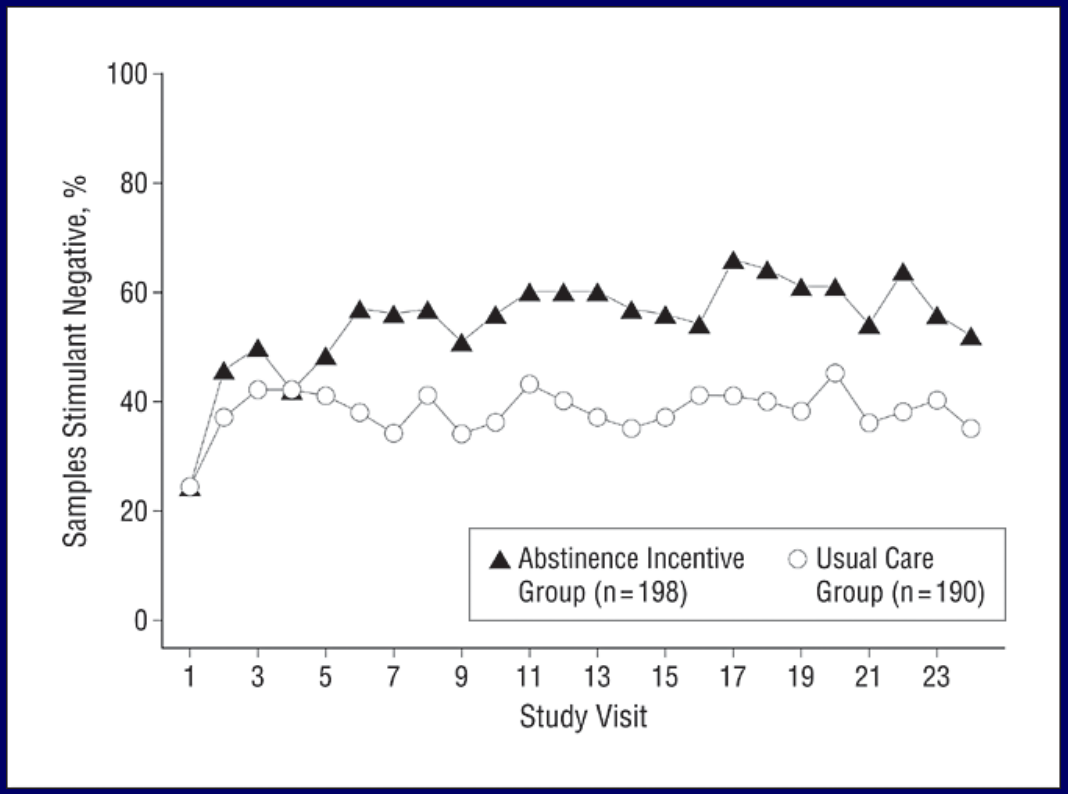
Contingency Management

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

Peirce et al. Arch Gen Psychiatry. 2006;63:201-208.

Contingency Management

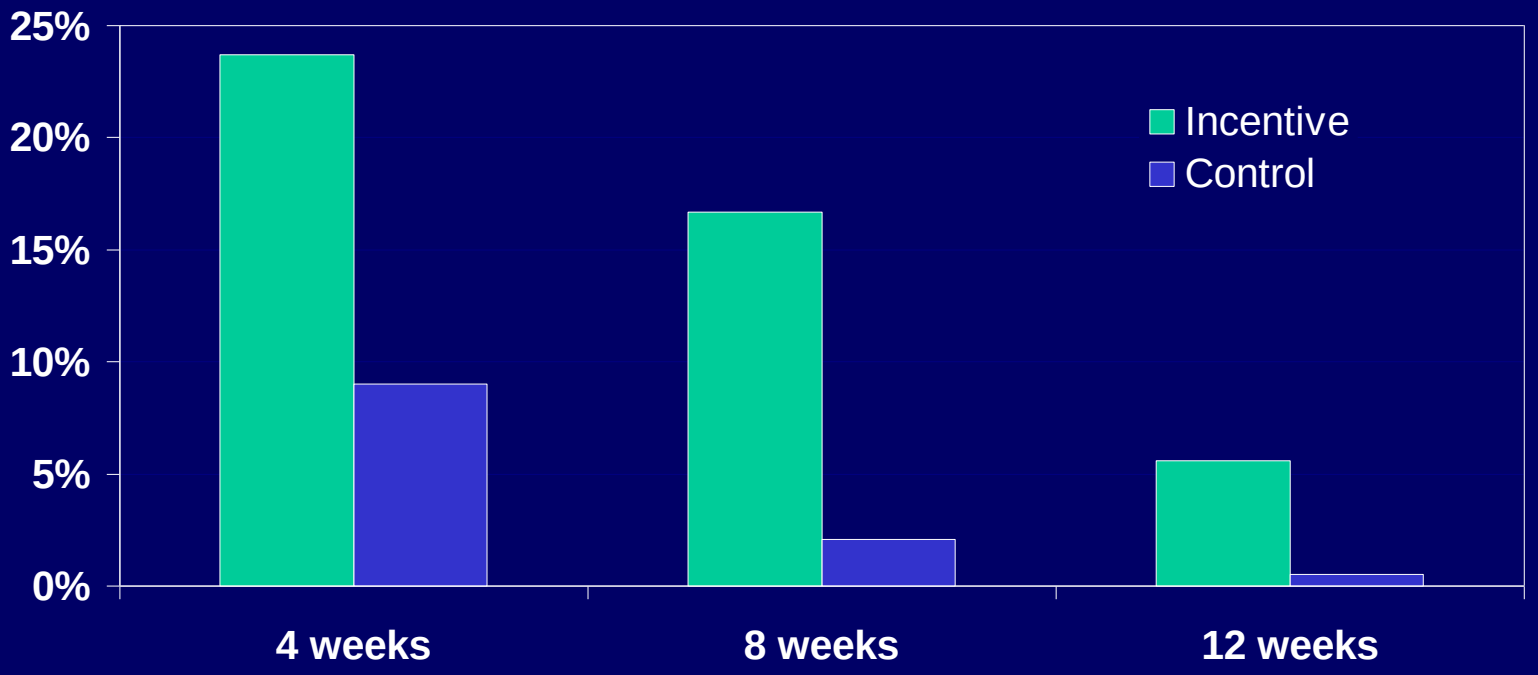


The mean percentage of submitted samples testing negative for target drugs (stimulants and alcohol) is shown for abstinence incentive and usual care participants at each of 24 study visits.

 Peirce et al. Arch Gen Psychiatry. 2006;63:201-208

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!

Alex Walley, MD, MSc
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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

JACC 2007: 50(7) e1-157.

Pharmacologic Treatment

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

- None proven effective

De Lima MS. Addiction. 2001: 97, 931-949.

5 things about stimulants

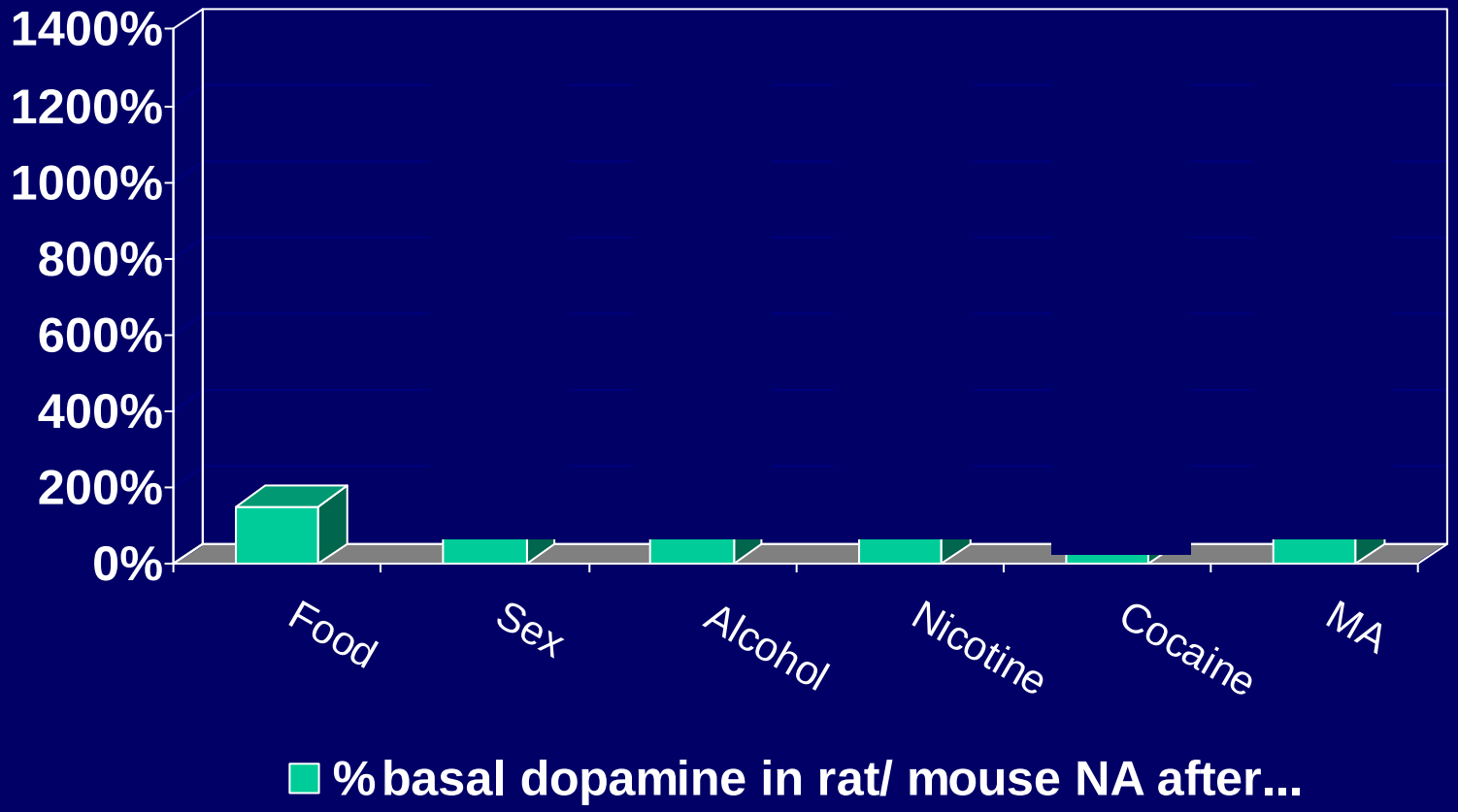
1. Easily available
2. Directly activate the mesolimbic pleasure center
3. Binge use often ends with dysphoria or lack of funds
4. Social and medical consequences
5. Treatment can work if you can find it

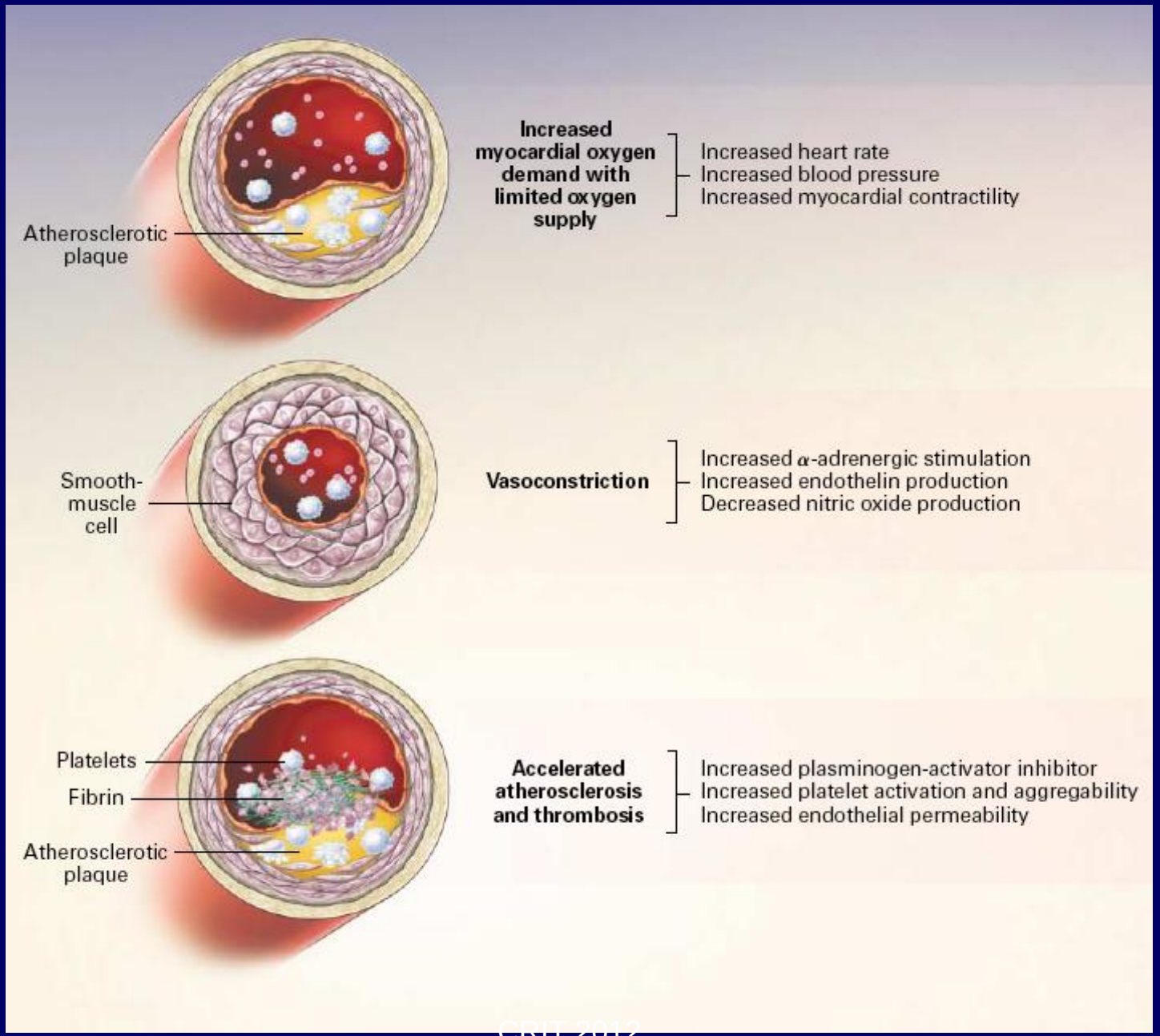
Learning objectives

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

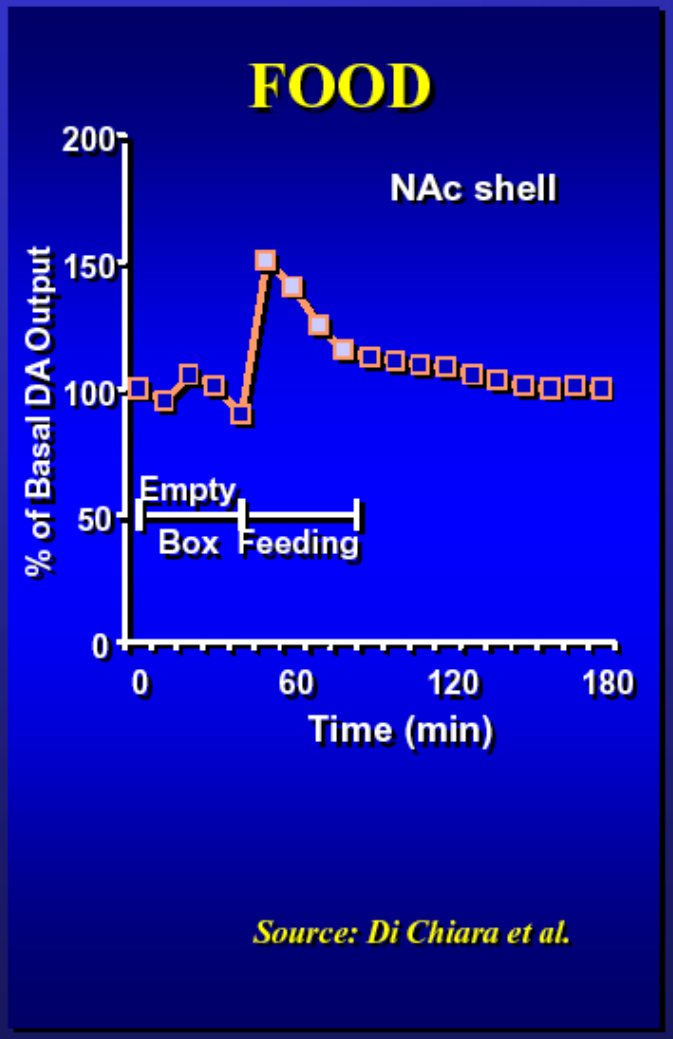
Dopamine release: nucleus accumbens

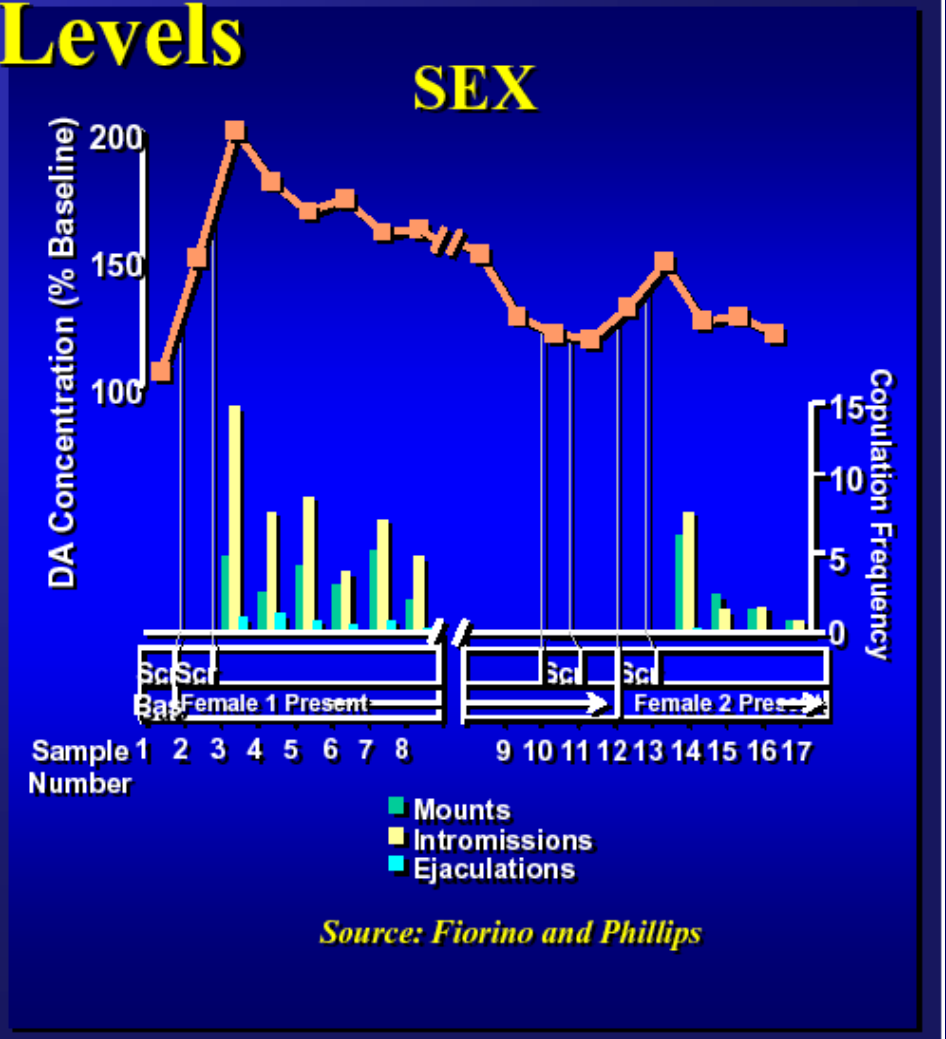




Lange, R. A. and L. D. Hillis (2001). "Cardiovascular complications of cocaine use." N Engl J Med **345**(5): 351-8.

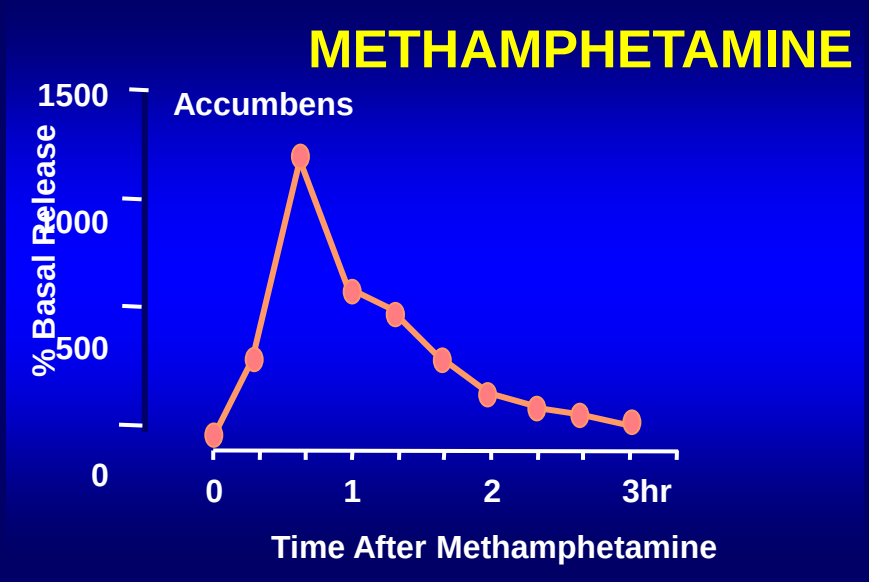
Natural Rewards Elevate Dopamine Levels

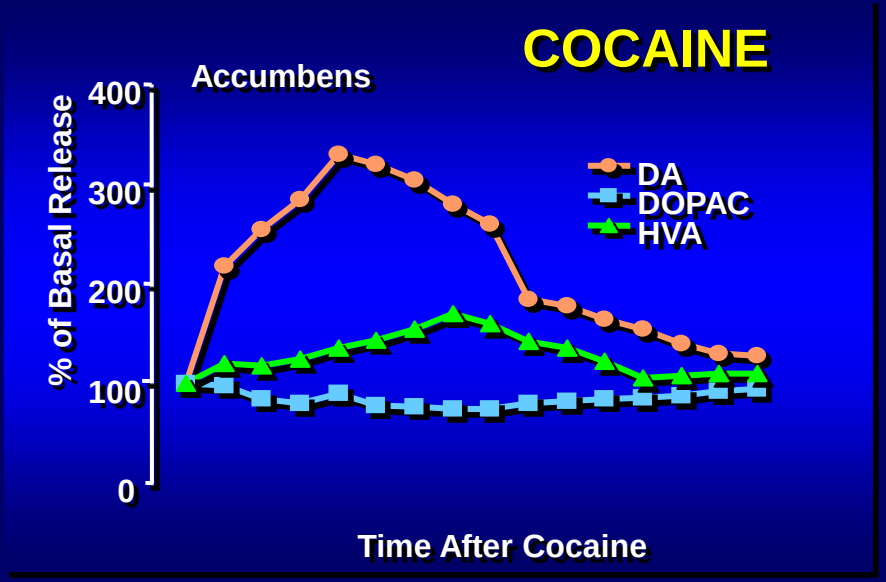


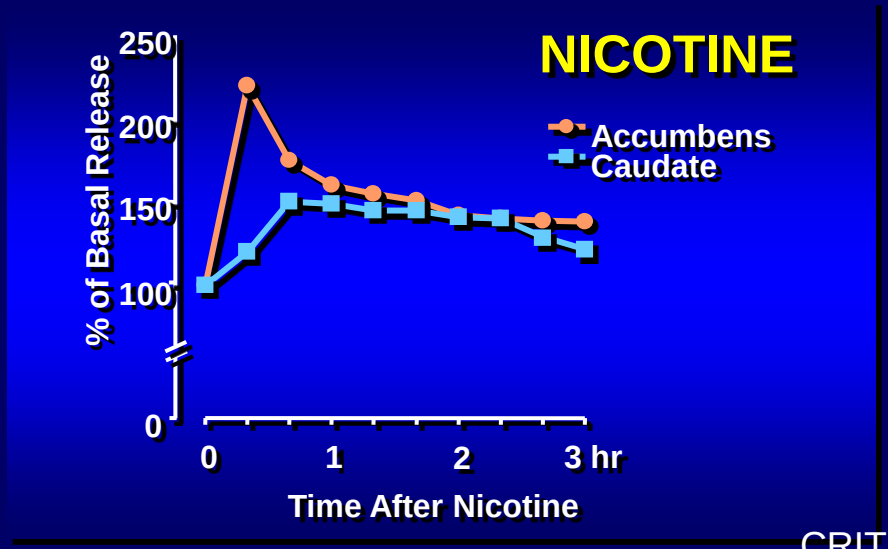


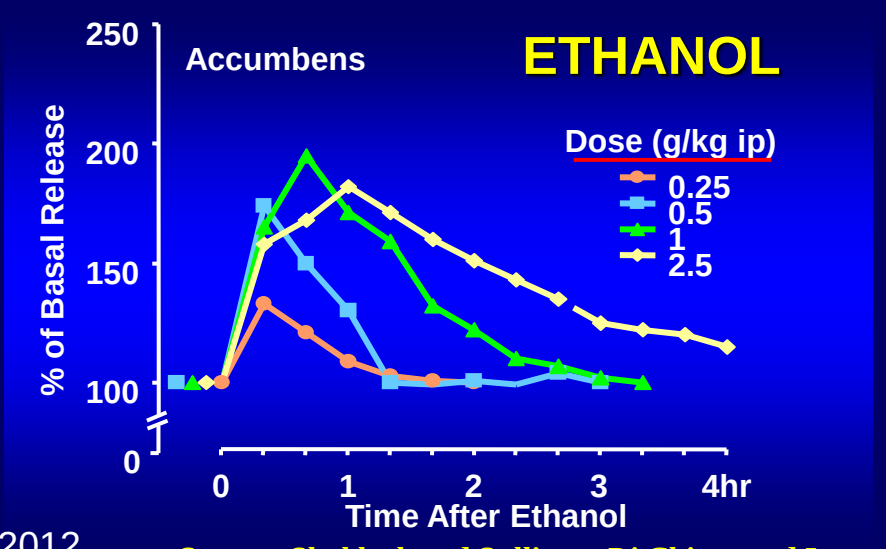
Slide from Richard Rawson

Effects of Drugs on Dopamine Release









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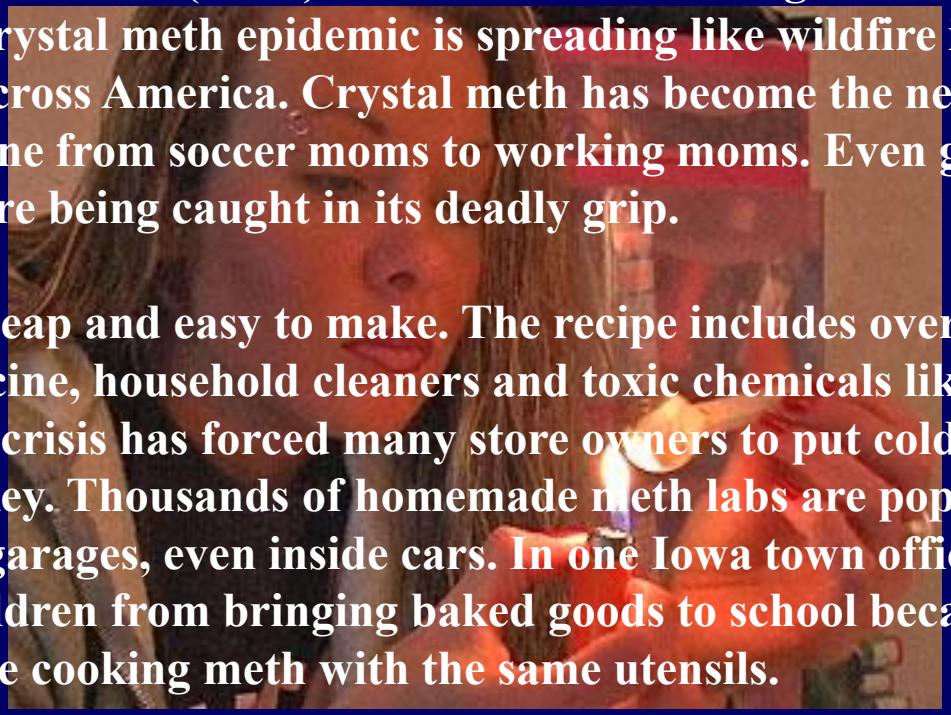
Source: Shoblock and Sullivan; Di Chiara and Imperato

Slide from Richard Rawson



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.

Will She Choose Life or Death?

An Oprah Winfrey Show Intervention

May 13, 2005

Chantel looks like an all-American 17-year-old girl. Her mother is a teacher's assistant and her father sells insurance. She works at an espresso shop. But she's addicted to crystal meth. Chantel and her family live outside Granite Falls, Washington.

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."

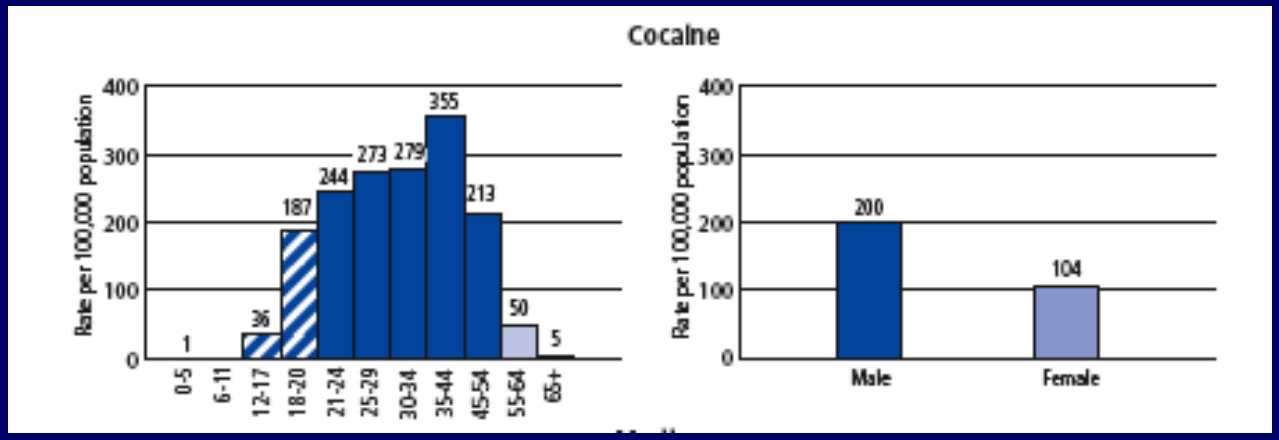
On one occasion, Chantel says she stayed up for 13 straight days, getting high every 20 minutes. "Meth makes you have this burst of energy," she explains. "And if you keep smoking it, you'll keep that energy burst." Was she worried about overdosing during that two-week binge? "You don't worry about anything,"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

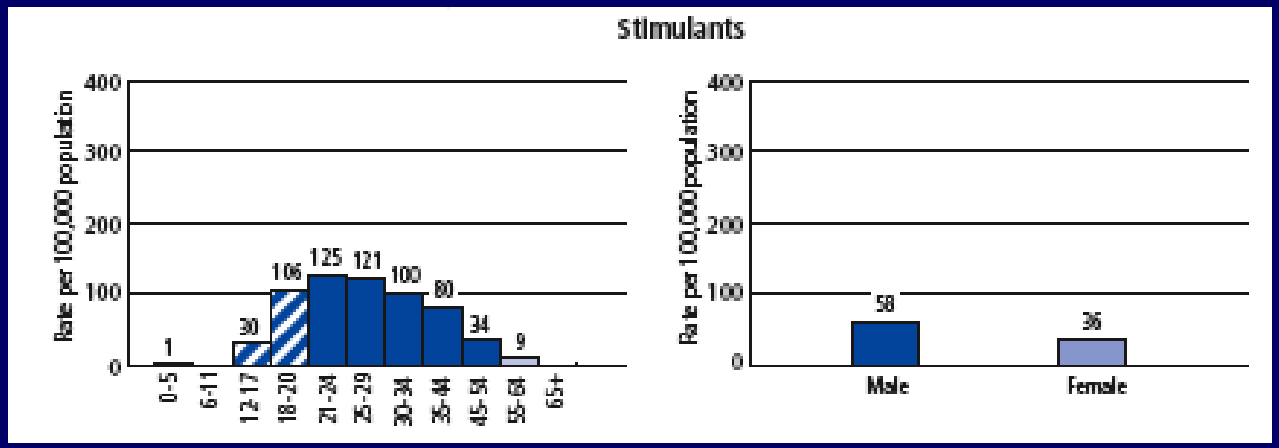
Pregnancy

- 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

Cox et al. Obstet Gynecol. 2008;111:341-7.

2005 drug-related ED visits





CRIT 2012 Drug Abuse Warning Network 2005 Report

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 ≥55% and no wall motion abnormalities).

Yeo K-K, et al. *Am J Med*. 2007;120(2):165–171.

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

Yeo K-K, et al. *Am J Med*. 2007;120(2):165–171.

“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 0z 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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www.totse.com/en/drugs/speedy_drugs/howtomanufactu172921.html

Treating Methamphetamine Dependence Reduces Risk for HIV

Rawson RA, et al. *J Subst Abuse Treat.* 2008;35(3):279–284.
Summary by David A. Fiellin, MD

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

Rawson RA, et al. *J Subst Abuse Treat.* 2008;35(3):279–284.

Results

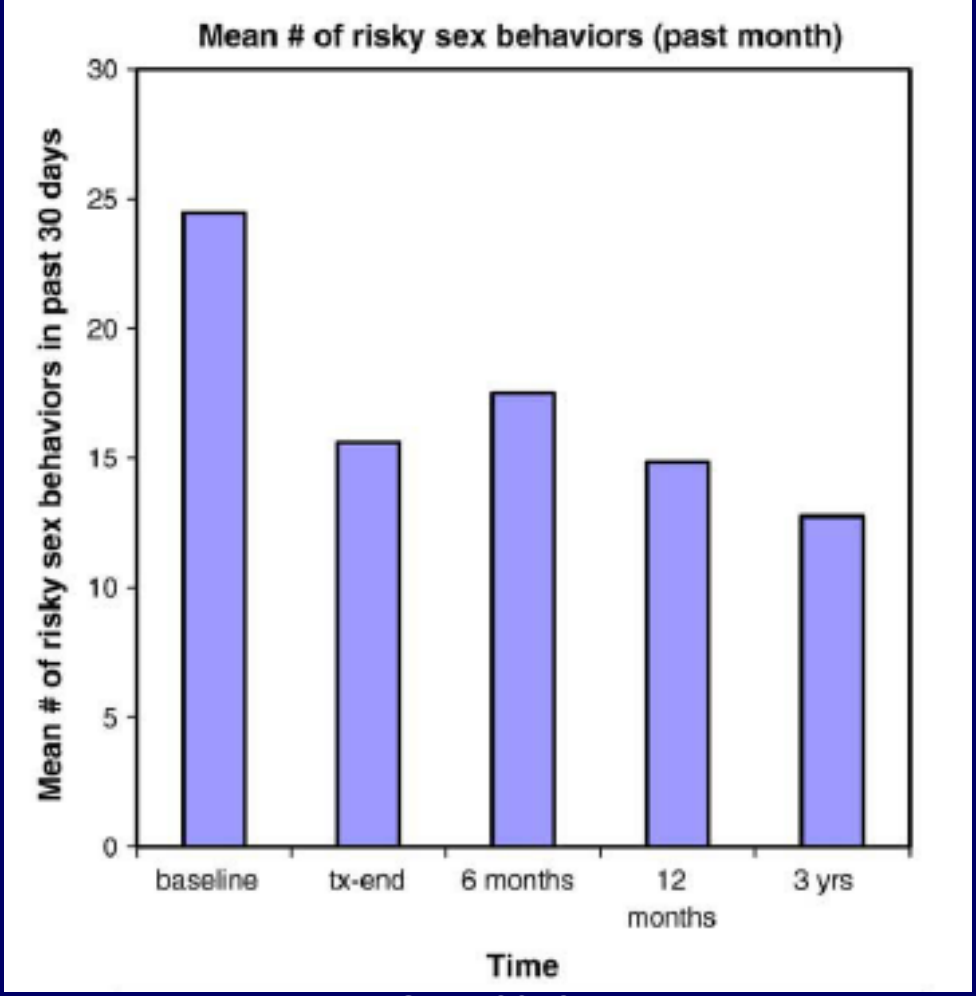
- The proportion of the sample who reported injecting methamphetamine within the previous 30 days declined significantly (14.6% to 5.4%) from baseline to discharge
- High-risk sexual activity also decreased:

	Baseline	Discharge
Mean times participants reported having sex without a condom	14.7	13.2
Mean times participants reported having sex without a condom with a methamphetamine user	2.3	1.4
Mean times participants reported having sex without a condom with an injection drug user	6.5	1.4
Mean times participants reported having sex while high	9.1	4.9

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

Rawson RA, et al. *J Subst Abuse Treat.* 2008;35(3):279–284.

Results – long term follow-up



N=569

Rawson RA, et al. *J Subst Abuse Treat.* 2008;35(3):279–284.

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.

Rawson RA, et al. *J Subst Abuse Treat.* 2008;35(3):279–284.

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 Chaisson. JAMA. 1989 Jan 27;261(4):561-5.

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

Swanson SM, et al. *J Trauma*. 2007;63(3):531

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).

Swanson SM, et al. *J Trauma*. 2007;63(3):531

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

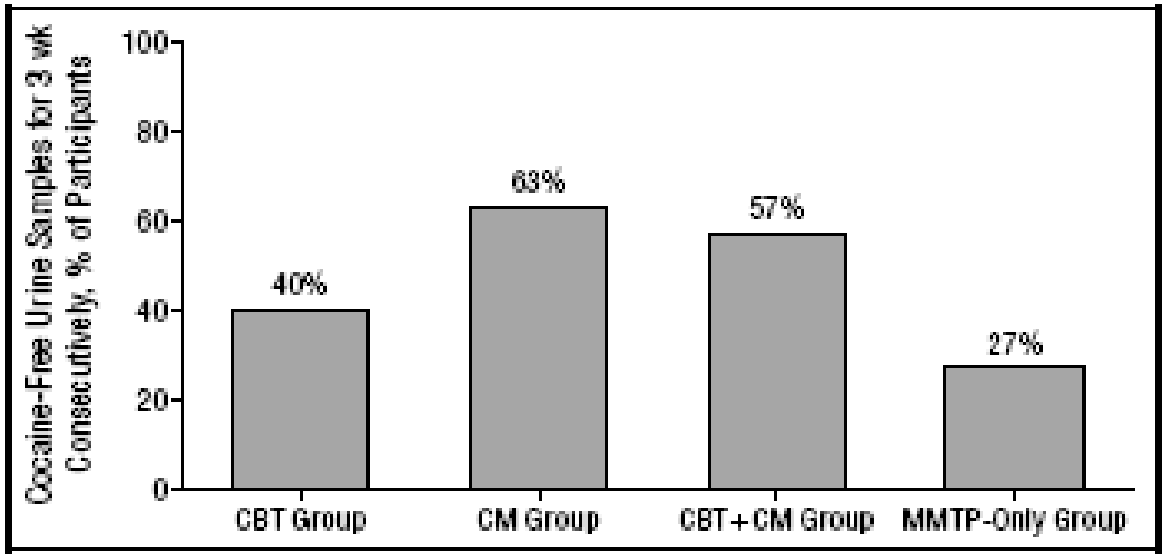


Figure 5. Percentage of patients achieving 3 consecutive weeks of cocaine-free urine samples by group ($\chi^2_3 = 9.9$; $P = .02$). CBT indicates cognitive-behavioral therapy; CM, contingency management; and MMTP, methadone maintenance treatment program.

Rawson et al. Arch Gen Psychiatry. 2002

Cognitive Behavioral Therapy

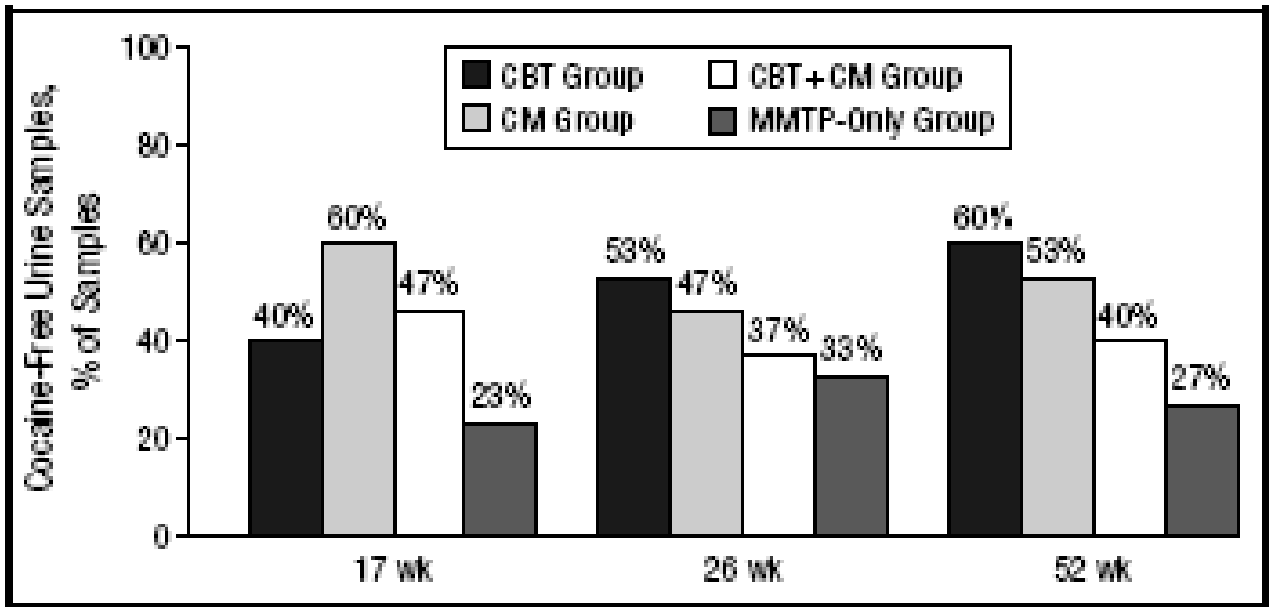


Figure 6. Percentage of 30 possible cocaine-free urine samples at the 17-week, 26-week, and 52-week follow-up points. CBT indicates cognitive-behavioral therapy; CM, contingency management; and MMTP, methadone maintenance treatment program.

Rawson et al. Arch Gen Psychiatry. 2002