

Stimulants: Cocaine and Methamphetamine

CRIT program
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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

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 options are limited

History

History: Cocaine



- From erythroxyton coca leaves in Andes
- Leaves chewed for thousands of years as stimulant
- 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

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When he sits before
Temptation

... prescribe
Desoxyn[®]
HYDROCHLORIDE
(Methamphetamine Hydrochloride, Abbott)

THE SYMPATHOMIMETIC AMINES HAVE BEEN found of value when administered under the supervision of a physician, or an officer in the direct management of obesity. The chief action of these drugs in this condition is the stimulation of appetite, which is due to the effect of the drug on the central nervous system, especially on the ascending limb of the cerebral. In addition to moving the appetite, Desoxyn imparts a feeling of well-being and increases mental and physical activity in such a way as to relieve the feeling of frustration and boredom which is often the underlying factor in overeating.

SMALLER DOSEAGE, LONGER EFFECT. IT IS CON- siderably agreed that *l-d*-amphetamine, although by itself, is insufficient alone to produce the sympathetic stimulation desired, is achieved with a smaller dose, the result of effect is more rapid and the duration longer. Some reporting these recommendations may produce side effects that attenuate the benefits of stimulation. With ordinary doses, little or no significant gross effect has been observed.

Desoxyn should not be relied upon to induce weight reduction but should be used only under the direction of a physician in conjunction with the prescription of a general hygienic regime and a normal diet.

DOSEAGE, SIDE EFFECTS.—THE DOSE OF DESOXYN must be adjusted in accordance with the requirements and response of the individual patient. When the maximum effect of the drug is desired, an adjusted dose is an absolute program. Desoxyn should be administered on a full stomach before meals, for other purposes the evening effects of the drug might not be desired; in some cases, Desoxyn should be administered with meals or immediately after meals.

Usually, the initial dose should be 2.5 to 5 mg. two to three times daily. Larger doses may be required in some cases, and should be arrived at cautiously. They may be continued as long as the desired results can be secured and there are no untoward effects. Individual oral doses in excess of 15 mg. are likely to produce unusual cardiac stimulation. Moderate is not recommended after a p.m. or at night, because of the possibility that the drug may interfere with sleep. If the patient is unable to sleep at night, the afternoon dose may be omitted or the preservative stimulation counteracted by the use of sedative medicine such as Nembutal.

OTHER INDICATIONS. DEPRESSIVE STATES. Desoxyn Hydrochloride is indicated for the administration in the treatment of depressive states and more of mild depression, anorexia, or the inhibition of feeling of well-being and increased energy will probably be produced in the patient. This means are not limited to any one of the following conditions for more complete therapy.

Acceptable results have also been reported following the use of *l-d*-amphetamine hydrochloride as an adjunct to the treatment of postoperative Parkinson's syndrome, chronic ataxia and generally in reactions for which amphetamines indicate the best of benefit.

ADVERSE REACTIONS. Desoxyn, as well as its salt, remove stimuli, *l-d*-amphetamine. Hydrochloride may cause stimulation of the patient but will not affect the drug, amphetamine. The drug has not been of benefit in the treatment of a patient's growth.

INDICATIONS.—DESOXYN HYDROCHLORIDE should be used with caution in the treatment of patients with cardiac disease, known hypertension, arteriosclerosis or in persons of advanced age. The drug is contraindicated also in persons with hypertension or in those who have shown sensitivity to epinephrine and its relatives.

DESOXYN PRODUCE EFFECTS SIMILAR to those produced by several amphetamines. Like the latter, it increases the rate of metabolism, increases the rate of work, increases the amount of energy and stimulates response and vigor in some persons. It does not produce the same marked peripheral vasoconstrictive effects of epinephrine and its relatives.

ONSET, PEAK, AND DURATION OF EFFECT WITH DESOXYN occurs in from 20 minutes to one hour. The duration of action of a single dose of 10 mg. usually varies from six to 12 hours, though in exceptional cases it may be noted for as long as 24 hours. There is a marked, but slight, fallowing a dose of 10 to 15 mg. at breakfast in some subjects. By dividing the dosage, patients may readily be treated. The duration of action increases the effect of the drug. Intensity of stimulative effect is somewhat greater in normal than in depressed or ataxic persons.

BLOOD PRESSURE, PULSE RATE AND RESPIRATORY rate usually are only slightly or temporarily affected, unless doses exceeding 10 to 15 mg. daily are taken.

THE PARENTERAL ADMINISTRATION OF DESOXYN Hydrochloride is suggested for relieving and maintaining blood pressure during operative procedures, particularly during spinal or regional block anesthesia. Its use is suggested for limited periods of anesthesia during surgical operations and for preoperative sedation, particularly before spinal anesthesia, in persons who manifest hypertension or who are resistant to poor surgical rates.

TOLERANCE NOT DEVELOPED, WHILE THE DRUG is not habit forming in the true sense of the word, some increased response may occur in cases of the stimulation, or normal subjects may be induced to use it in excess for relief of fatigue. Tolerance to the drug is not developed. The euphoric and waking effects decrease with prolonged use of the drug in excess of the recommended dose for sleep and rest. As a result, a larger dose is required to produce the desired effect for sleep, and it is the more that the patient the amphetamine consistency and mental effects. Withdrawal of the drug may cause a moderate depression. Administration of Desoxyn should be under the constant supervision of a physician.

1957

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he needs to
blow his top...

**WEIGHT
REDUCTION
WITHOUT
JITTERS**

AMBAR™ TABLETS AND EXTENTABS®

Weight Reduction: These patients may resist weight reduction because they fear losing the emotional security involved in overeating, hence Calentab or Tablets help them hold the diet line by giving them a more alert, brighter outlook. Ambar adds incentive to weight reduction, gives the patient a better chance of holding off the disabling effects of continued overweight.

Without Jitters: Methamphetamine, a more potent CNS stimulant than amphetamine, but producing less cardiovascular effect, is combined in Ambar with phenobarbital. The combination subdues CNS effects just enough to protect the patient from overstimulation. Result: mood exhilaration with no undesirable excitation—weight reduction without jitters.

Ambar Extentabs: 10 to 12 hours of appetite suppression in one controlled release, or several action doses.

Methamphetamine hydrochloride . . . 20.0 mg.
Phenobarbital (1 gr.) . . . 84.8 mg.

Ambar Tablets: for conventional dosage or sublingual use only.

Methamphetamine hydrochloride . . . 2.50 mg.
Phenobarbital (1/4 gr.) . . . 21.6 mg.

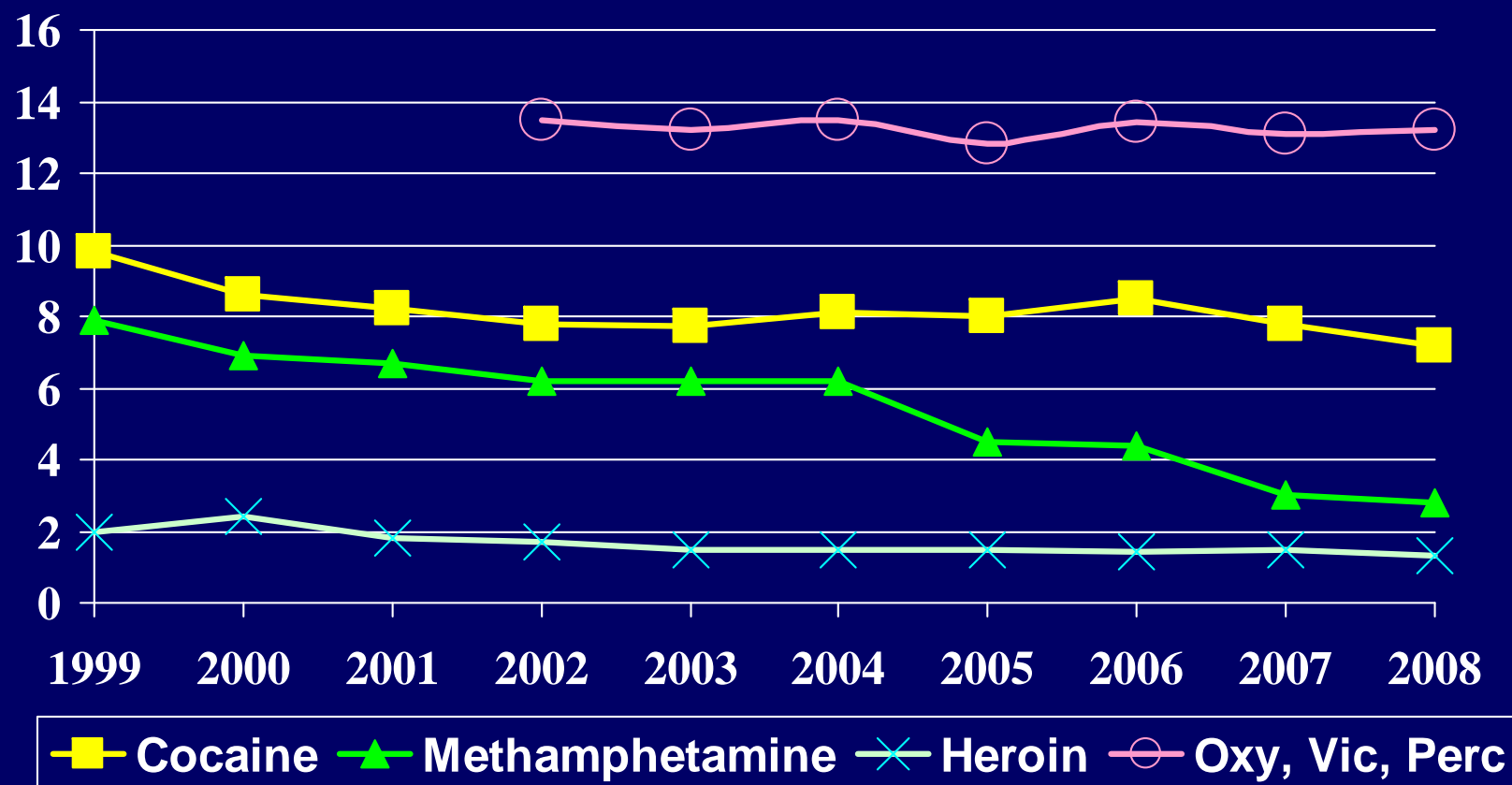
A. H. ROBBINS CO., INC.
Rutland 35, Virginia
Clinical Pharmacologists
of North Since 1878.

1959

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Epidemiology

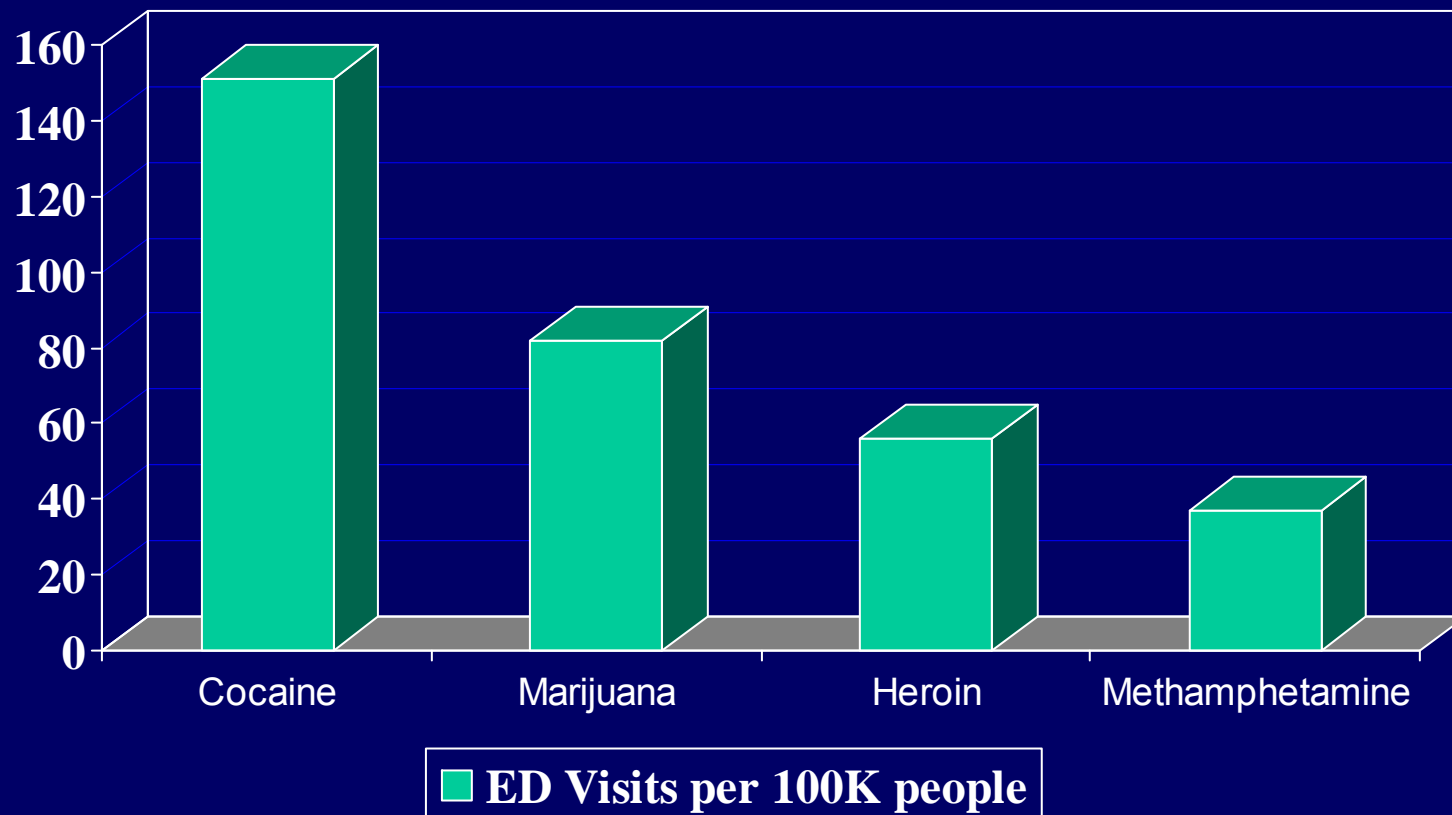
% lifetime use by 12th graders



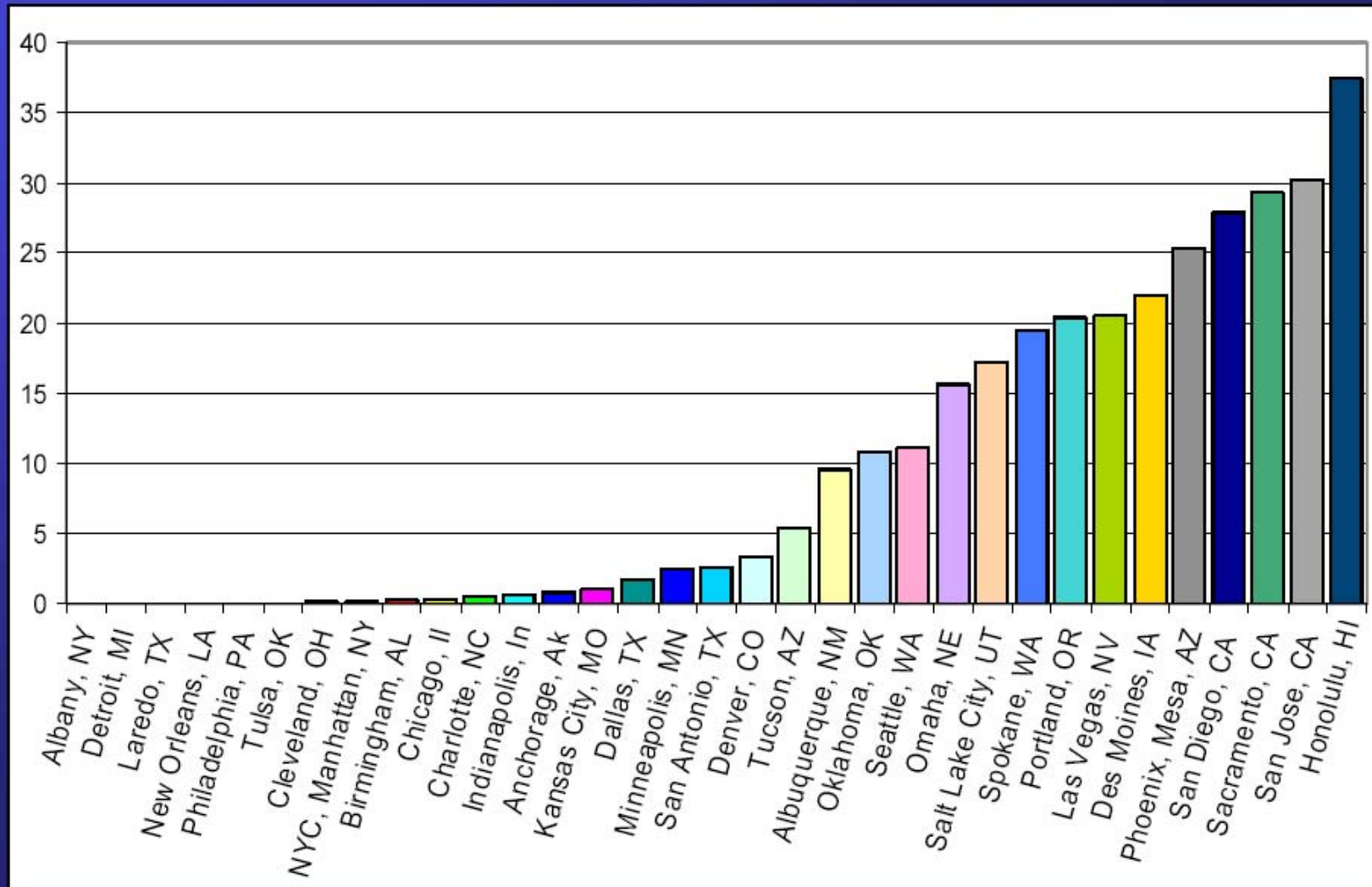
Monitoring the Future Study 2007

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2005 drug-related ED visits



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>

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“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:

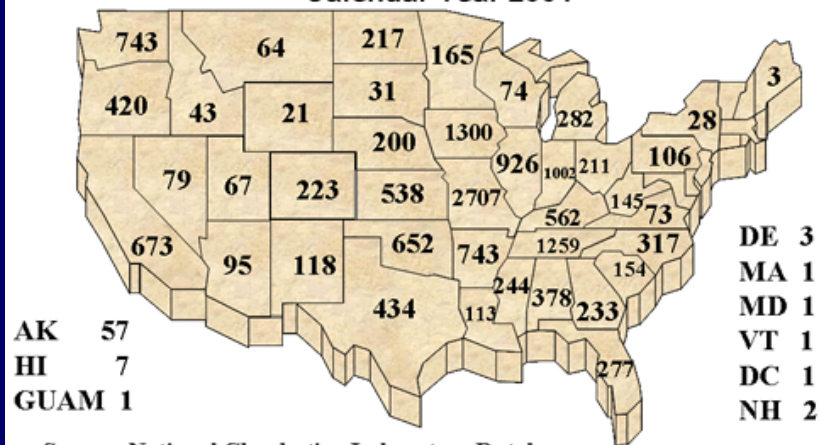
- 1 Case Regular Pint size Mason Jars (Used for canning)
- 2 Boxes Contact 12 hour time released tablets.
- 3 Bottles of Heet.
- 4 feet of surgical tubing.
- 1 Bottle of Rubbing Alcohol.
- 1 Gallon Muriatic Acid (Used for cleaning concrete)
- 1 Gallon of Coleman's Fuel
- 1 Gallon of Aceton
- 1 Pack of 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.”

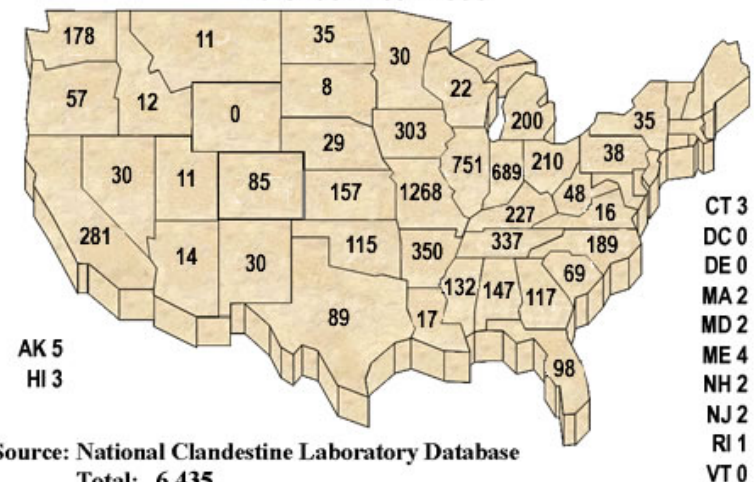
Clandestine lab incidents

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

Map last updated February 2007

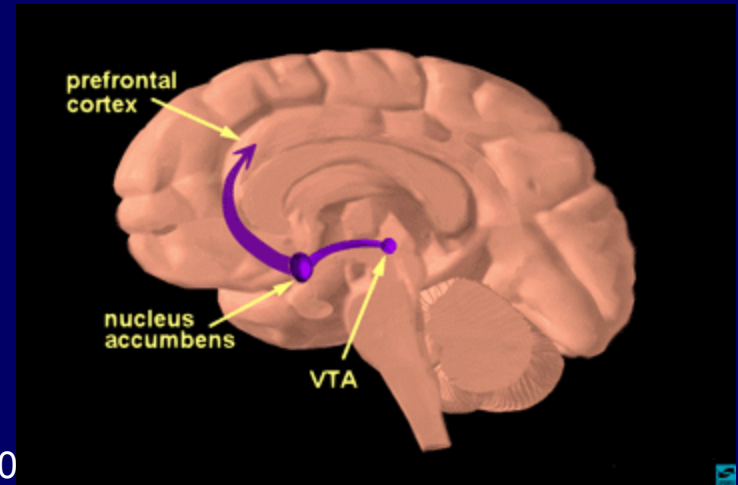
Stimulant Effects

Why do people use drugs?

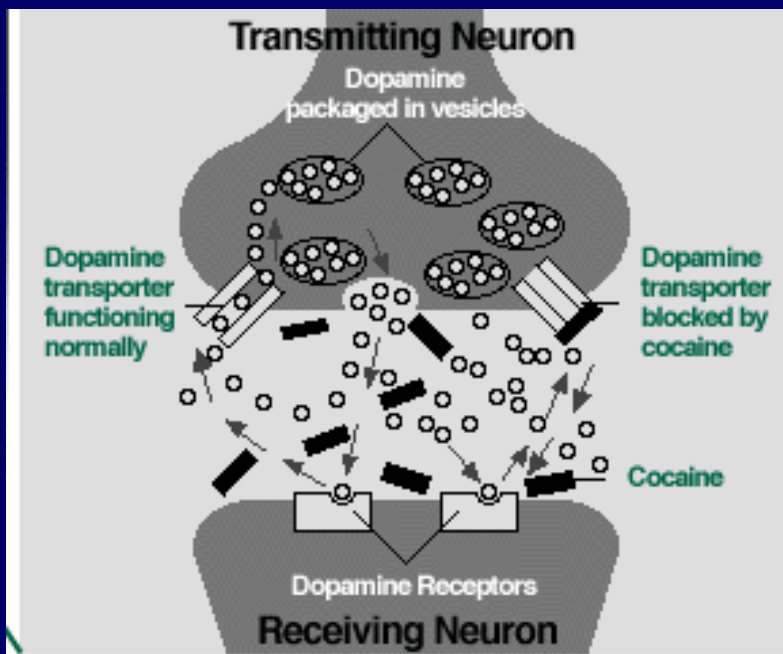
1. To feel good
2. To feel better

Why do people use stimulants?

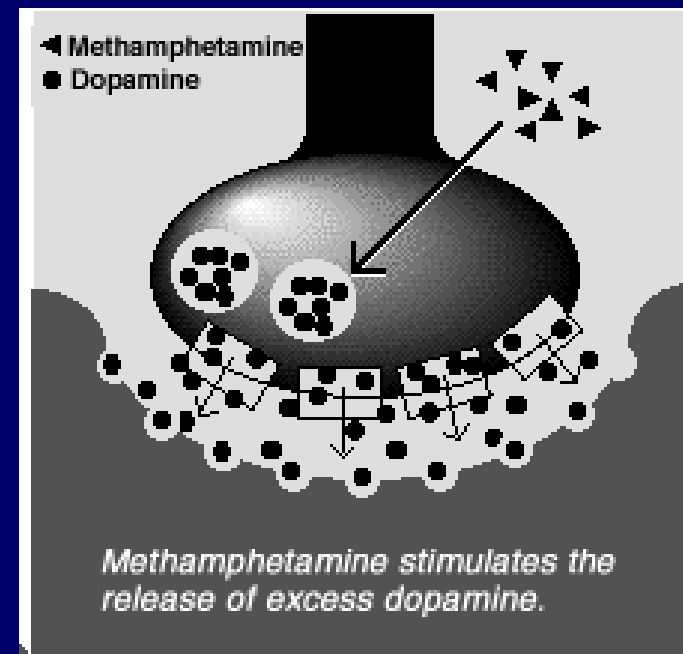
- Euphoria - Rush
 - Onset and intensity depends on delivery method
- Increased energy, alertness, libido
- Diminished social inhibition
- Decreased appetite



Cocaine



Methamphetamine



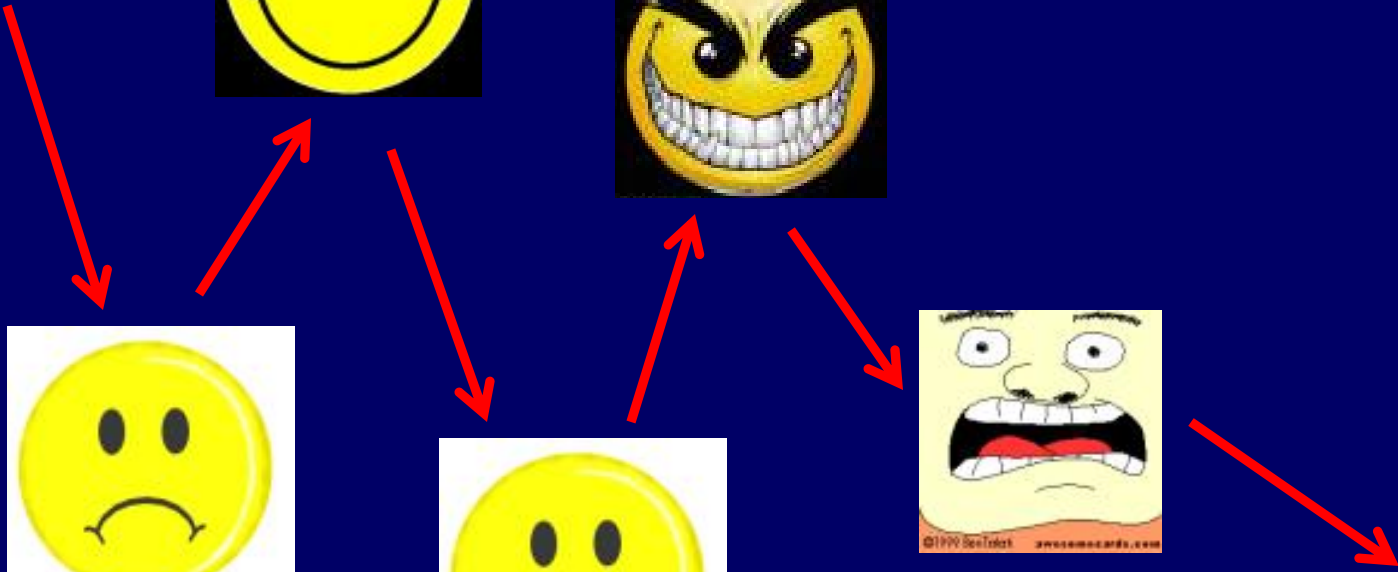
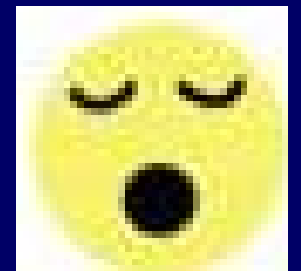
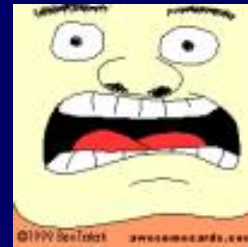
PK: Cocaine

	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



Binges

- 2-3 day binges are typical, called runs
- Regular redosing 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

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

Withdrawal dopamine depletion

- Intense craving
- Depression
- Fatigue
- Unpleasant dreams
- Hypersomnia, then insomnia
- Increased appetite
- Agitation/ anxiety/ paranoia
- Limited ability to experience pleasure

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

- Rhabdomyolysis
- Dehydration
- Acute Renal Failure
- Acidosis
- Hyperthermia

Skin

- Cellulitis/ abscess
- Excoriations
- Chemical burns

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 (Viagra) are 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

Cocaethylene

- Psychoactive substrate from EtOH+cocaine
- ETOH commonly used to “come down” from a cocaine binge
- 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

- 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.

Pharmacologic Treatment

- Dopaminergic
 - Disulfiram – Carroll. Arch Gen Psychiatry. 2004;61:264-272
- GABA modulators
 - Tiagabine – Gonzalez. Drug Alcohol Depend. 2007; 87: 1-9.
 - Topiramate
 - Baclofen – Heinzerling. Drug Alcohol Depend. 2006 Dec 1;85(3):177-84.
 - Vigabatrin (GVG) – Brodie et al. Synapse. 2005; 55: 122-5.
- Stimulant replacement
 - Modafinil – Dackis. Neuropsychopharmacology. 2005 Jan;30(1):205-11.
 - Methylphenidate
 - Bupropion
- Vaccine
 - Sofuoglu & Kosten. Expert Opin Emerg Drugs. 2006; 1: 91-8.
 - Gorelick & Gardner. Drugs. 2004; 64: 1547-73.

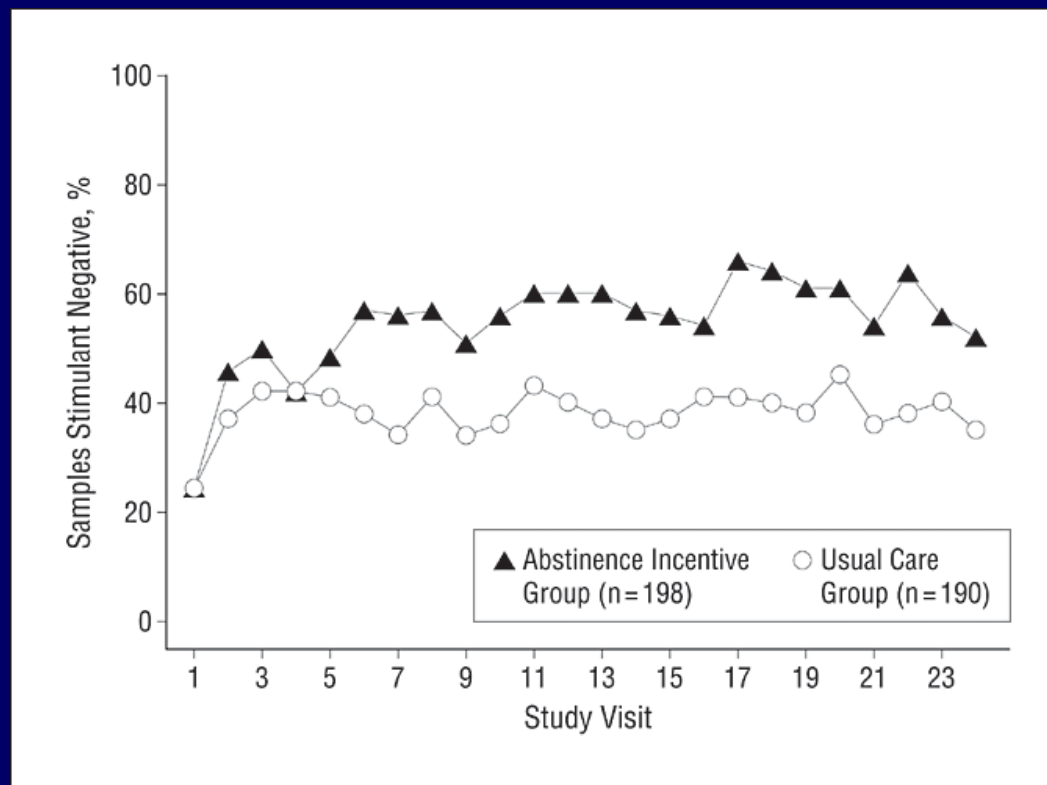
Non-Pharma Treatment

- Cognitive behavioral therapy
- Self-help/ 12 step groups
- Therapeutic communities
- Recovery houses
- Contingency management

Contingency Management

- 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

Contingency Management

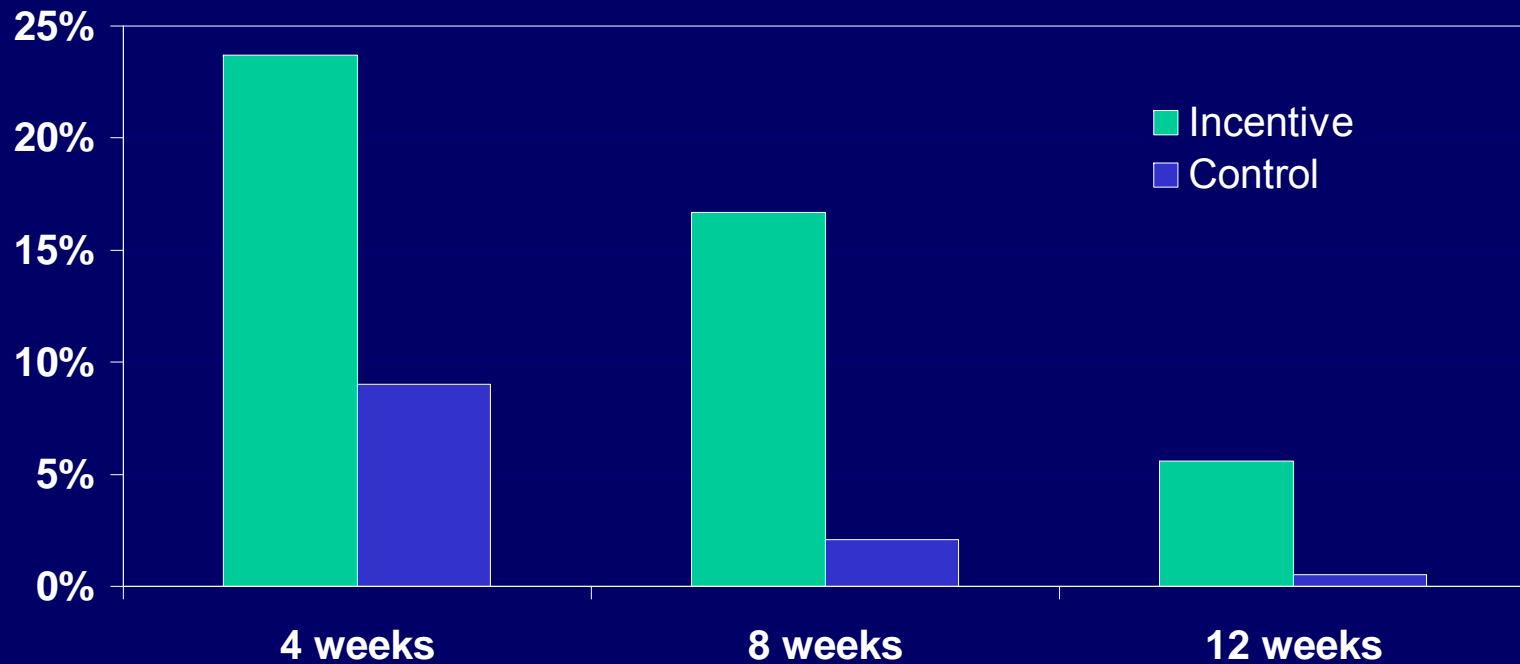


Target drug use. The mean percentage of submitted samples testing negative for target drugs (stimulants and alcohol) is shown for abstinence incentive and usual care participants at each of 24 study visits.

Pearce et al. Arch Gen Psychiatry. 2006;63:201-208.
CRIT Program 2009

Contingency Management

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



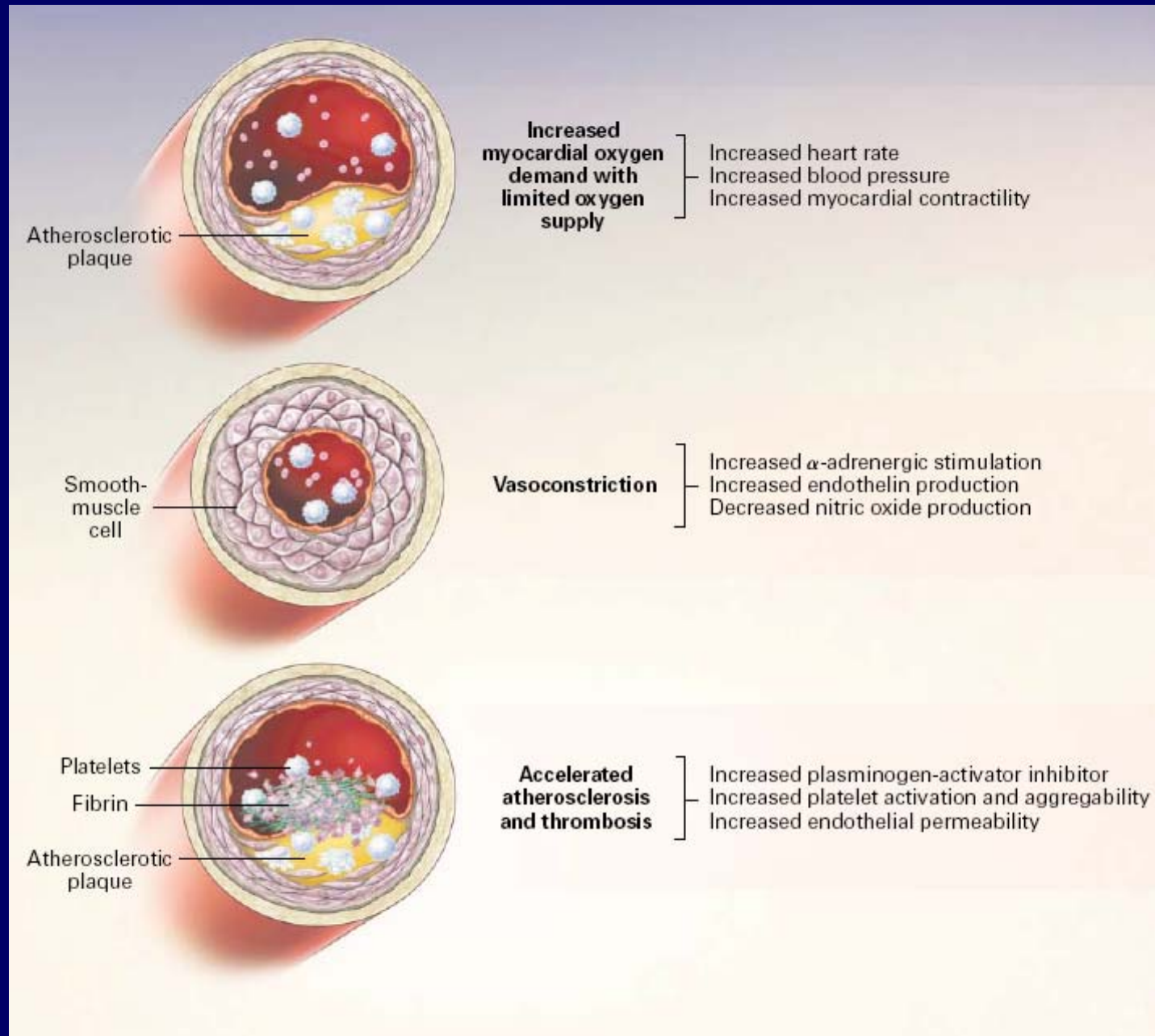
Average cost = \$1.46 per person/day

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

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Thanks!

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

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 \geq Risk
 - Increased HR or BP: Mixed alpha/beta blocker after vasodilator
- Class III: Risk \geq Benefit
 - No ST changes: Cath

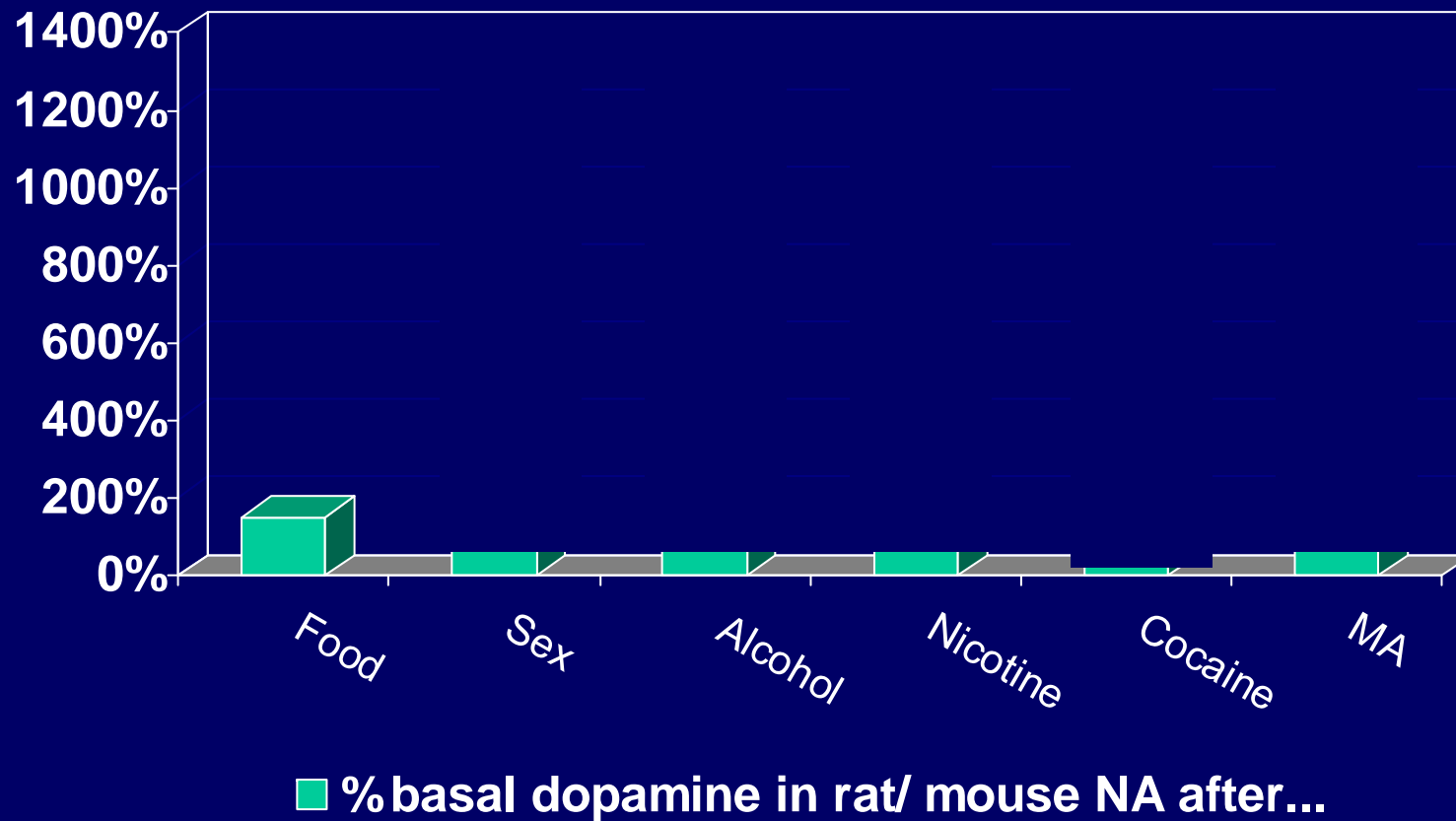
Note: Level of evidence is C “expert opinion” for all recommendations

AHA 2008 Scientific Statement on cocaine chest pain and MI

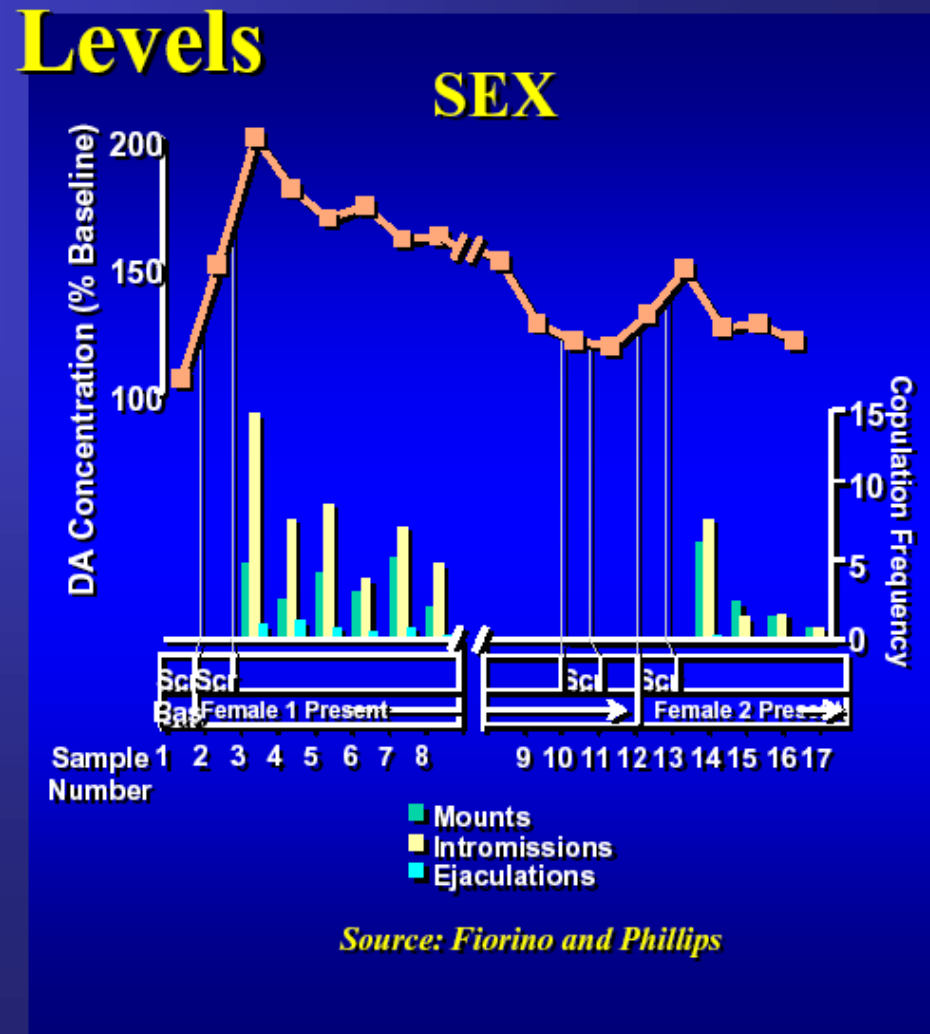
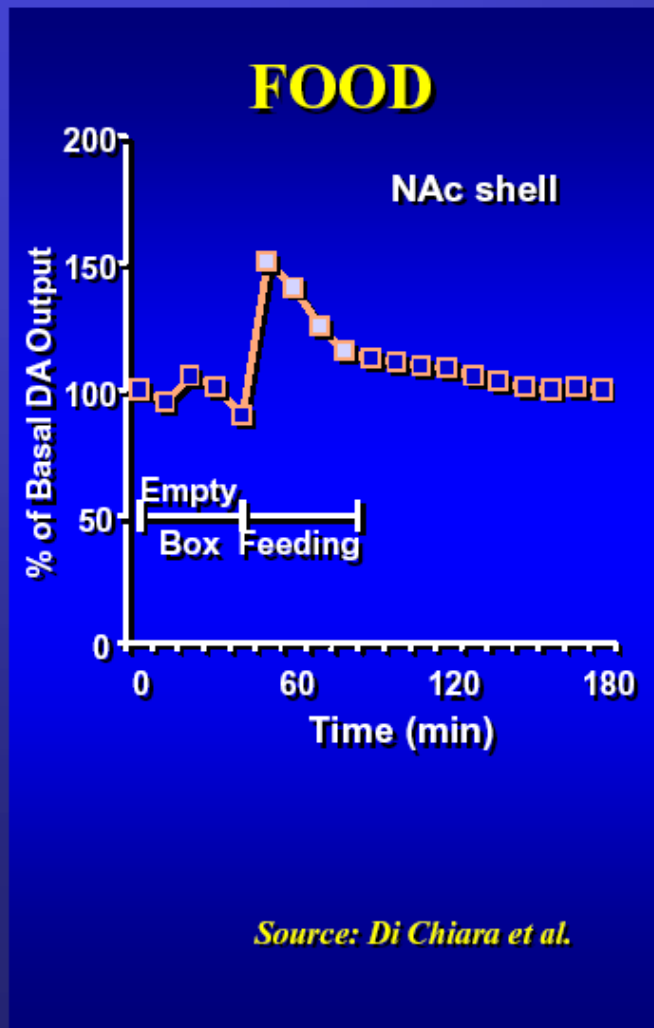
- Class I: Benefit \ggg Risk
 - Benzodiazepines (Level B)
 - ASA (Level C)
 - NTG (Level B)
- Class IIb: Benefit \geq Risk
 - CCB (Level C)
 - Phentolamine (Level C)
- Class III: Risk \geq Benefit
 - Beta-blockers (Level C)

McCord et al. Circulation. 2008; 117.

Dopamine release: nucleus accumbens



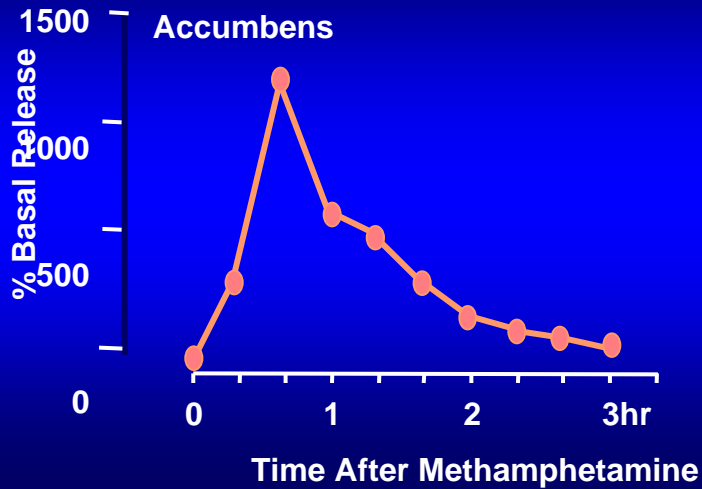
Natural Rewards Elevate Dopamine



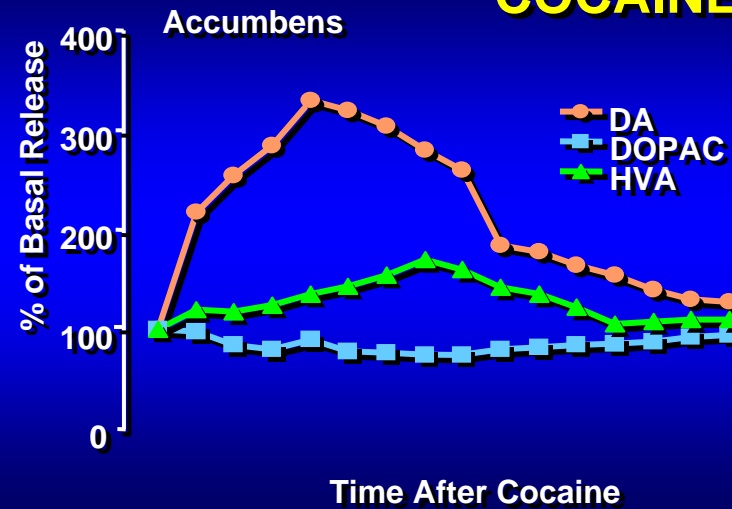
Slide from Richard Rawson

Effects of Drugs on Dopamine Release

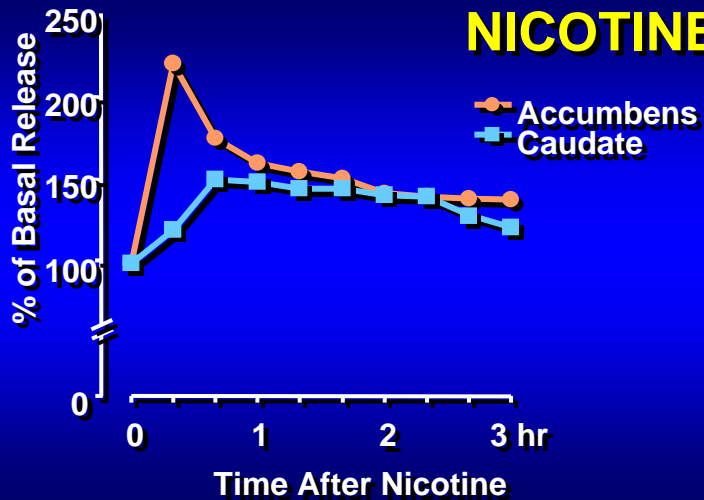
METHAMPHETAMINE



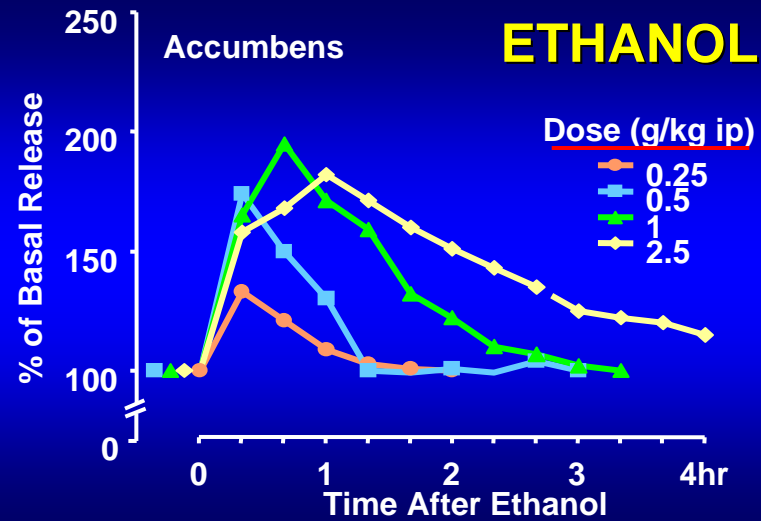
COCAINE



NICOTINE

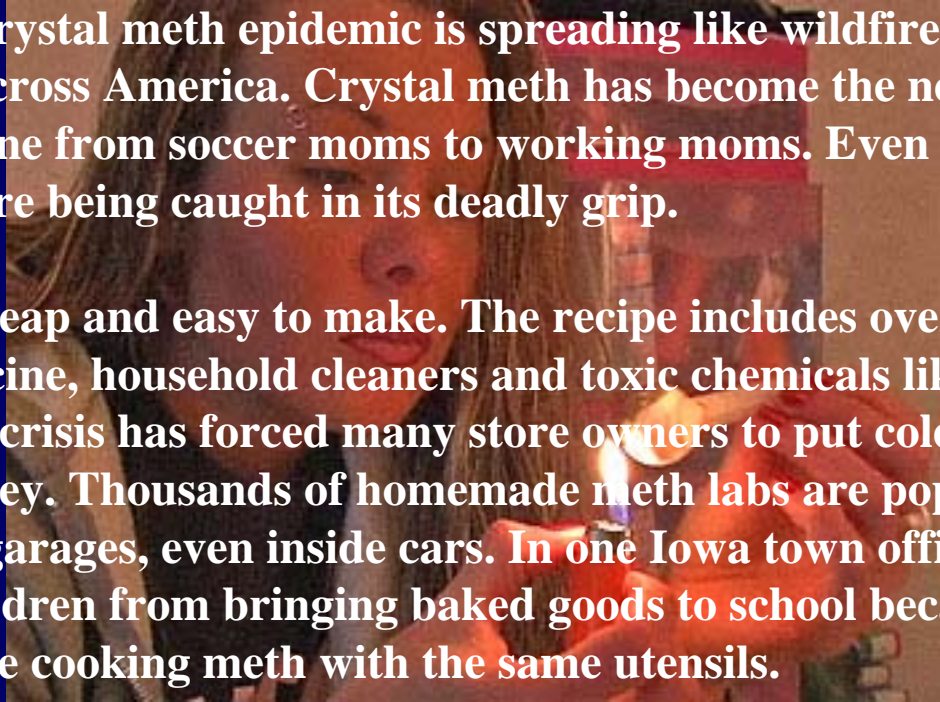


ETHANOL



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."

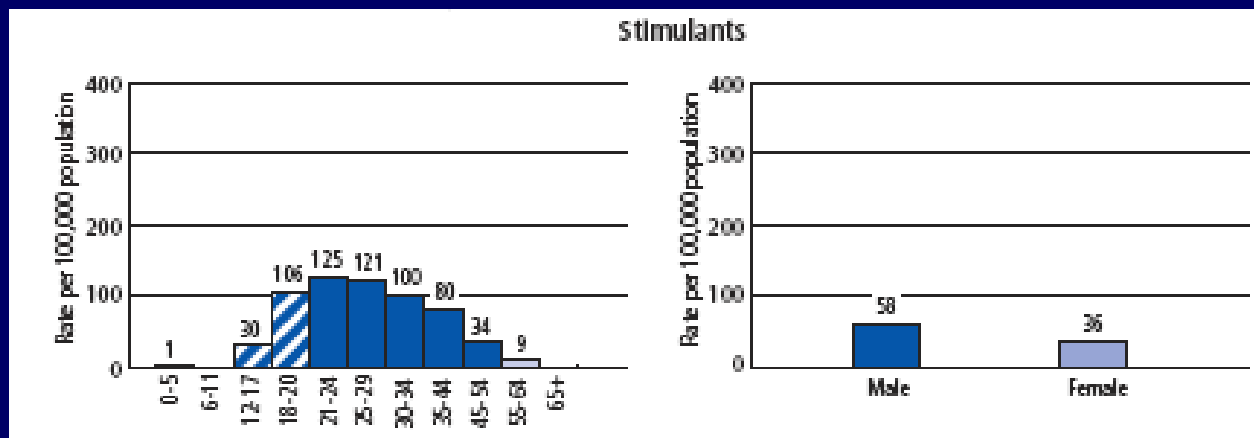
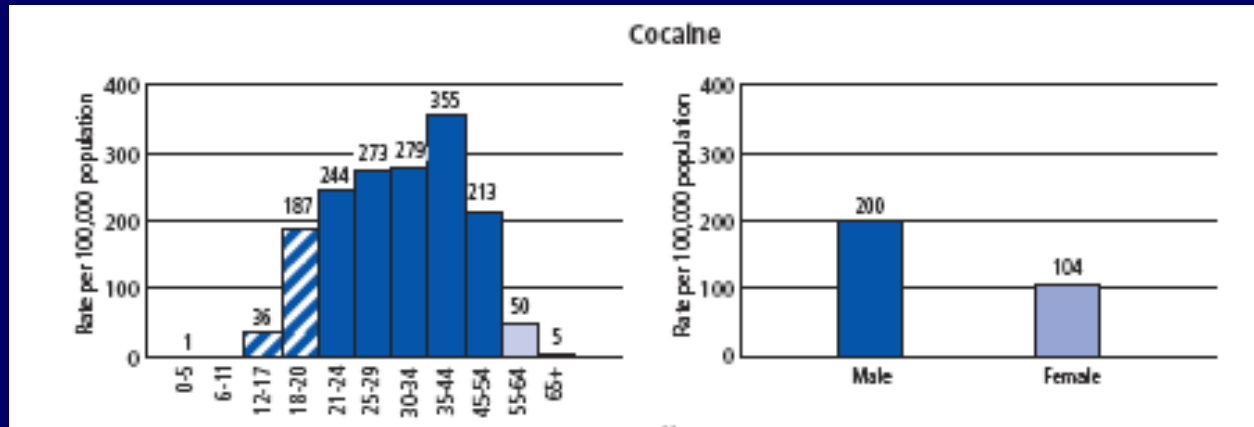
On one occasion, Chantel says she stayed up for 13 straight days, getting high every 20 minutes. "Meth makes you have this burst of energy," she explains. "And if you keep smoking it, you'll keep that energy burst." Was she worried about overdosing during that two-week binge? "You don't worry about anything,"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



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).

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.

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