Stimulants

Charles Dackis, M.D.

Pre-Lecture Exam Question 1

1. Which of the following is not known as a stimulant?

a. Methamphetamine

b. Buproprion

c. Methylphenidate

d. Lamphetamine

Pre-Lecture Exam Question 2

2. Which form of cocaine administration is the most effective route of administration?

a. Oral

b. Intrapulmonary (inhalation)

c. Intranasal

d. Subcutaneous

Pre-Lecture Exam Question 3

3. The cocaine withdrawal syndrome consists of which of the following?

a. Anergia
b. Mood depression
c. Hypersomnia
d. Nausea
e. None of the above
f. a, b, and c

Pre-Lecture Exam
Question 4

4. There is no evidence from controlled trials that the following medication is useful in enhancing cocaine abstinence:

a. Topiramate

b. Paroxetine

c. Disulfram

d. Modafinil

Pre-Lecture Exam Question 5

5. Previously, and to this day, cocaine has been used legally for medicinal and recreational purposes. Which statement is true?

a. Chewing coca leaves is highly addictive and is a major health problem in South America.

b. Coca Cola originally contained 100 mg of cocaine per bottle.

c. Cocaine wine was used primarily to induce sleep.

d. Cocaine has analgesic properties.

Outline

A. Historical Use of Cocaine
B. Cocaine Toxicity
C. Development of Cocaine Addiction
D. Cocaine Craving and Associated Phenomena
E. Cocaine Withdrawal
F. Neurobiologic Aspects of Cocaine
G. Cocaine Phenomenology
H. Treatment of Cocaine Dependence-
   Psychosocial, Psychopharmacologic
I. Conclusions

Teaching Points

- To discuss the phenomenology of cocaine dependence and addiction
- To discuss cocaine toxicity
- To discuss promising treatments for cocaine dependence

Stimulants

Cocaine

Methamphetamine

Dextroamphetamine

Methylphenidate

Others

Cocaine History

The leaf of the coca plant has been chewed for thousands of years

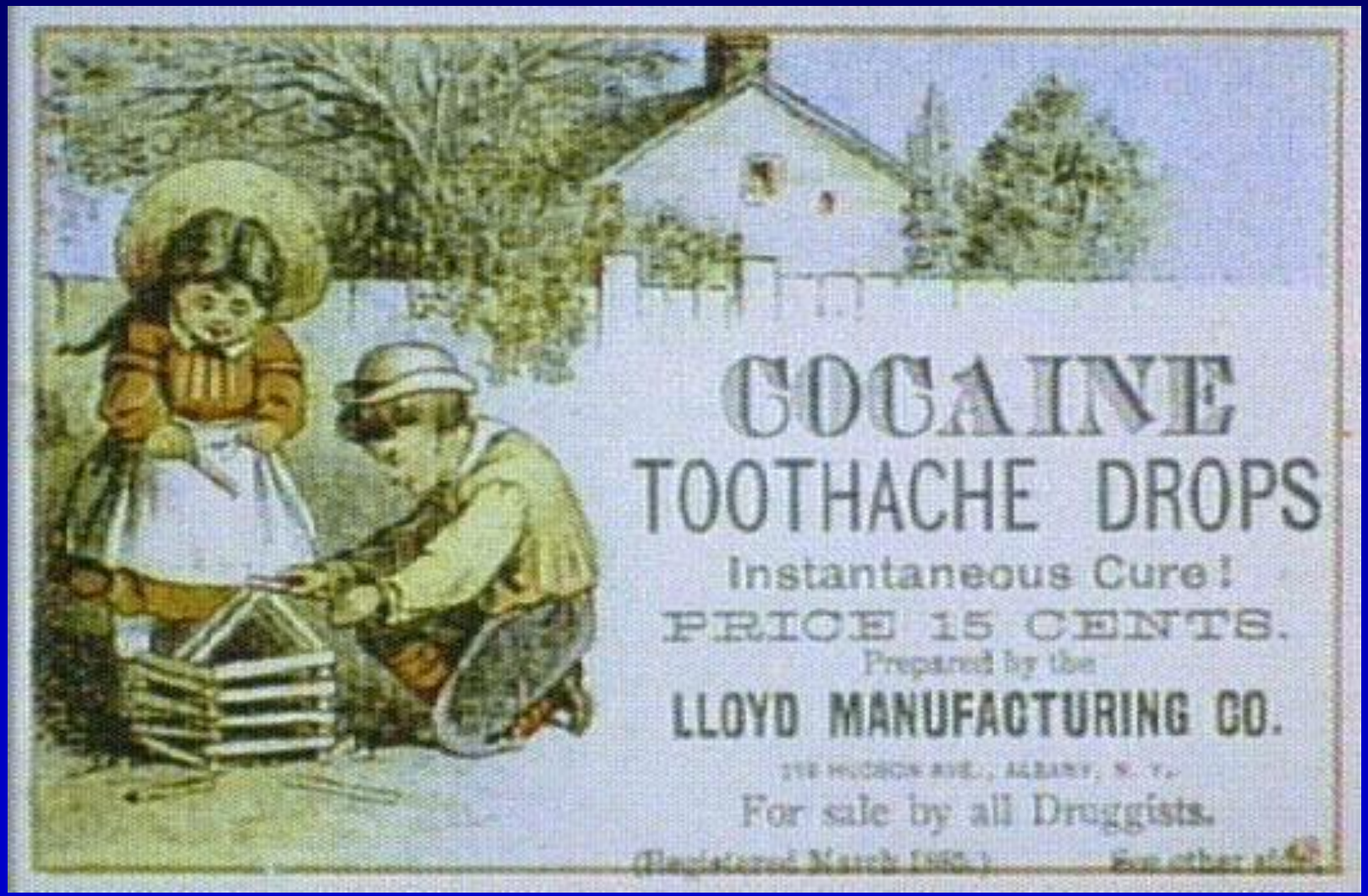
Cocaine History

Coca wine had medicinal as well as recreational uses.

Cocaine History

Celebrity endorsements were common then as they are now. There was little if any perceived risk.

Cocaine History



Cocaine found its way into a number of different products

Cocaine History - A Household Drug

Coca Cola originally contained 10 mg of cocaine

It was sold in "dope shops"

Cocaine Epidemiology

Perceived Risk & Supply

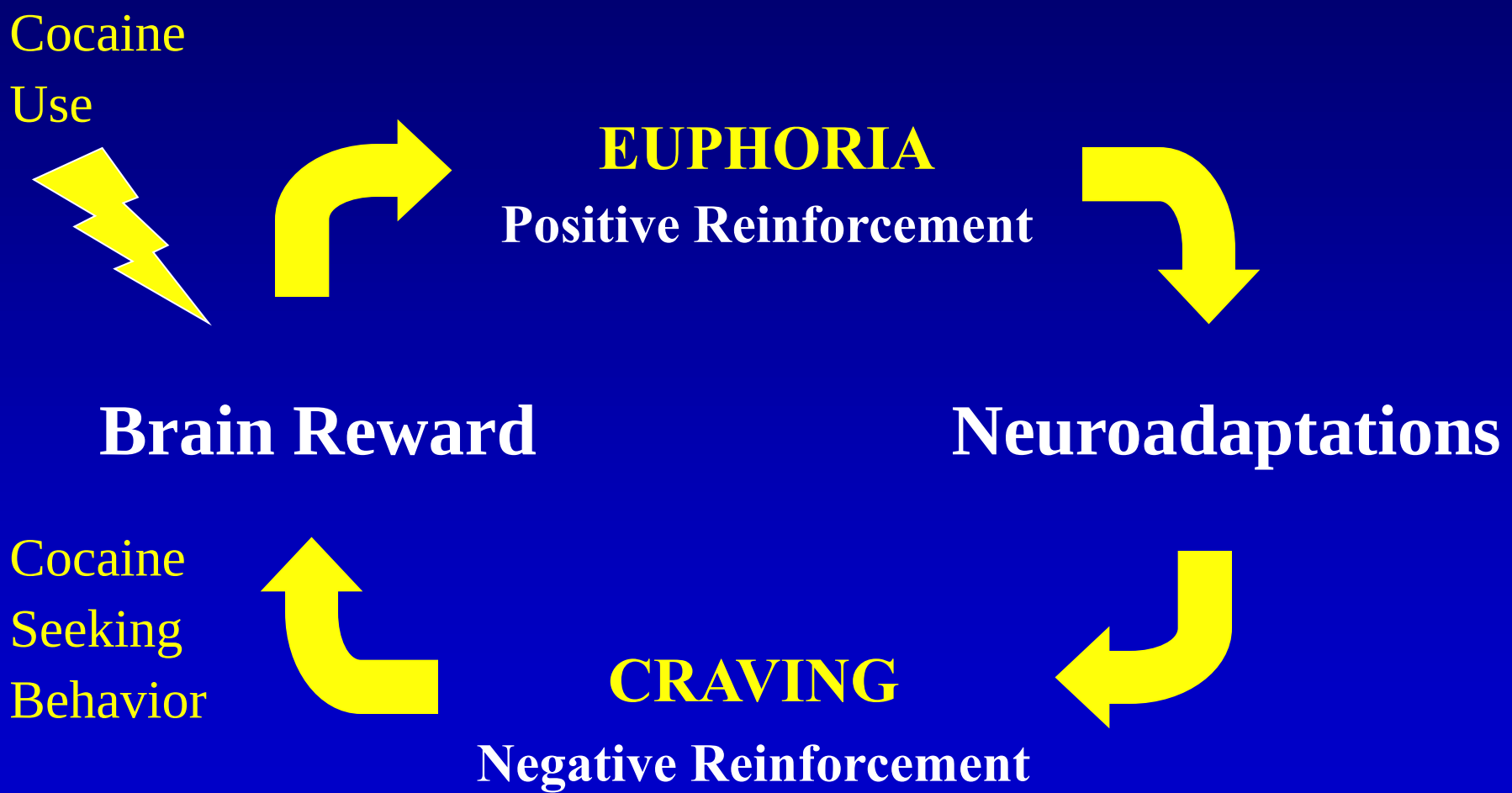
The key determinants of stimulant epidemics

Stimulant "epidemics" driven by low **perceived risk** and increasing **supply**, occurred initially with cocaine, later with amphetamine, and again with cocaine in the 1980s.

Education can address perceived risk but law enforcement efforts to limit supply have not been particularly successful

Cycle of Cocaine Addiction

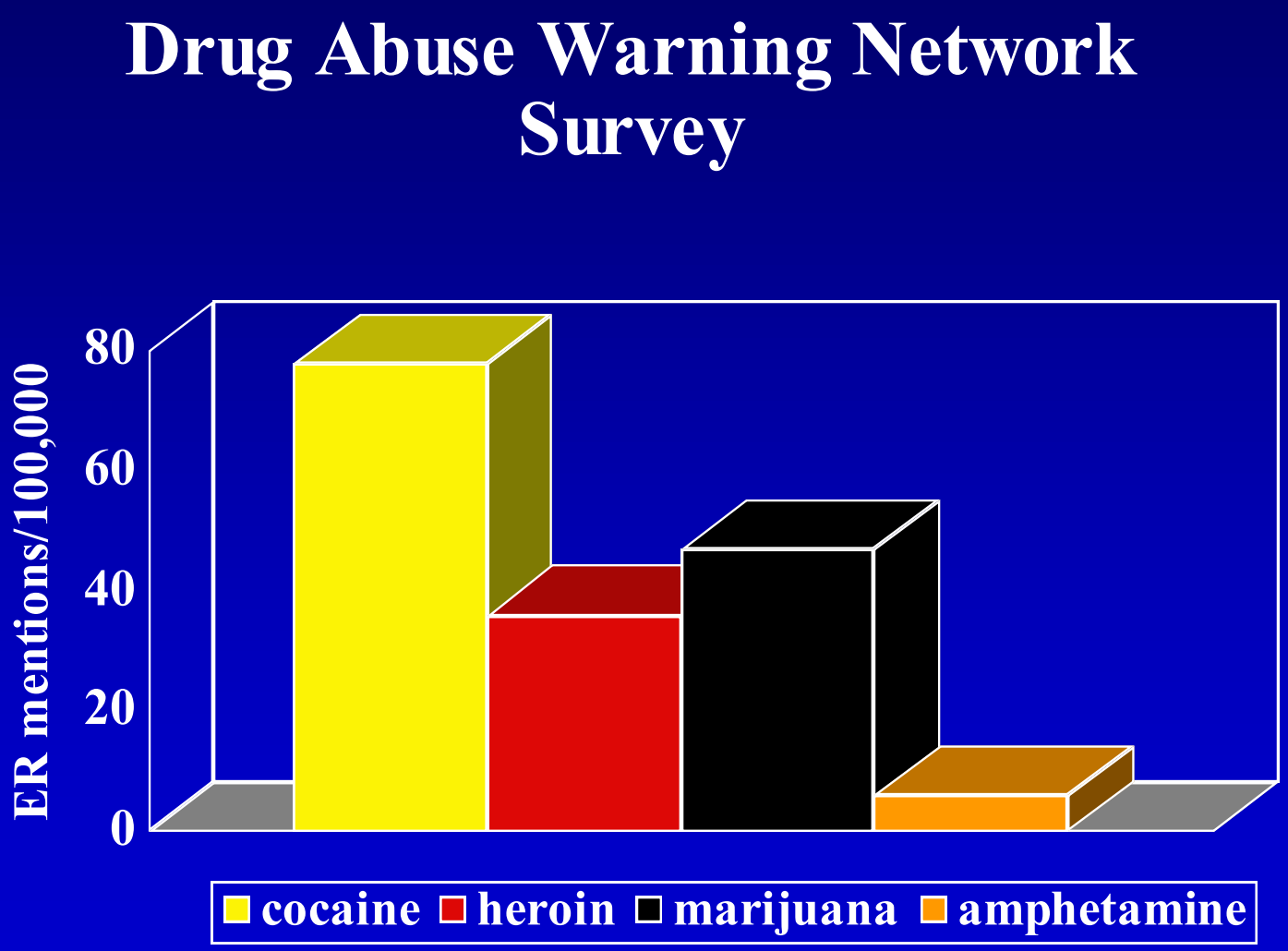
This addiction has biological, behavioral & psychological aspects



Treatment interventions are designed to reduce euphoria & craving

Toxicity

Cocaine is the most common illicit drug mentioned in ER reports.



Toxicity

Toxic effects of cocaine result from:

- Vasospasm (MI, CVA)
- Electrophysiological effects
  - Seizures
  - Cardiac arrhythmias
- Hypertension (bleeds)

Toxicity

Cardiac complications of cocaine use:

- Angina
- Myocardial infarction
- Cardiomyopathy
- Myocarditis

Toxicity

Other medical problems:

- Hyperpyrexia
- Intestinal ischemia
- Renal failure
- Perforated nasal septum
- Low birth weight, spontaneous abortion
- Psychosis/Depression/Anxiety

Amphetamine Toxicity

Methamphetamine

- –Overtaking cocaine on the West Coast
- –Significantly more neurotoxicity than cocaine

Prescription Stimulants for obesity

- –Short-term adjuncts
- – Long-term abuse liability (Adderall)

ADD

Toxicity: Cocaine Use with Alcohol and Heroin

- Cocaine & alcohol
  - Most common cocaine combination
  - Reduces anxiety
  - Cocaethylene is psychoactive and cardiotoxic
- Intravenous cocaine & heroin (speedball)
  - Enhanced euphoria positive effects of both drug
  - Reduction of unpleasant cocaine effects
  - Medical complications associated with IV use

Clinical Syndrome

Cocaine Euphoria

Cocaine-Induced Craving

Cue-Induced Craving

Stress-Induced Craving

Baseline Craving

Cocaine Withdrawal

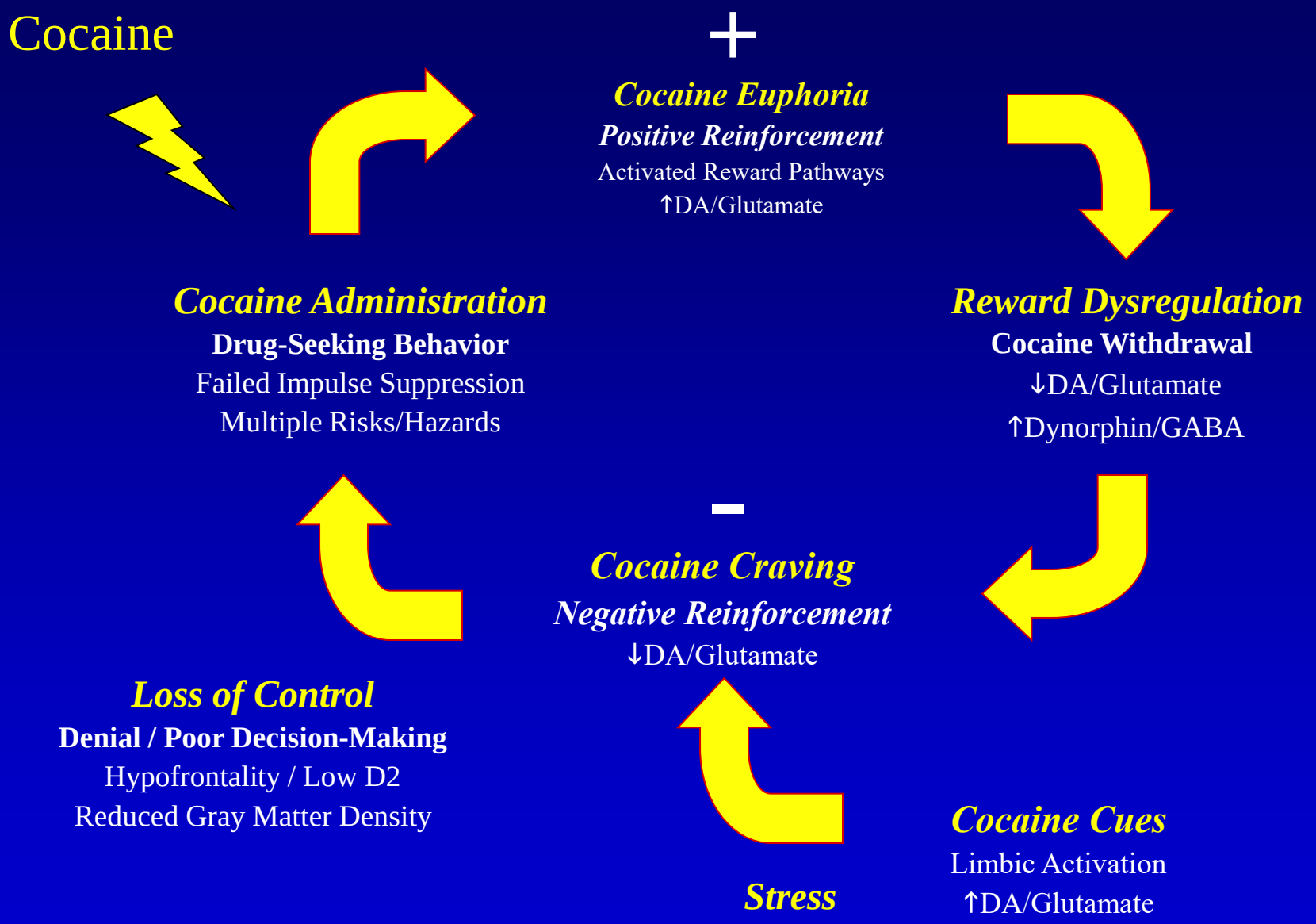
Hedonic Dysregulation

Hypofrontality

These clinical components occur at different time points during active addiction and recovery

Their psychological, behavioral and neurochemical aspects that can be targeted by psychosocial and pharmacological interventions

Dynamic Cycle of Cocaine Addiction



Cocaine Euphoria

Brief duration

- Gives way to craving in minutes
  - (even when levels are still elevated)
- Lack of satiation - multiple doses
- Binge pattern use

Intensely rewarding

- Animals self-administer till death
- Patients obsessed with euphoria

Distinctive features v. heroin/alcohol

- Manic-like, racing thoughts, energy, vigilance
- Psychomotor activation, environmental focus

Neurobiology of Cocaine Euphoria

↑DA Neurotransmission

Imaging studies demonstrated correlate cocaine euphoria with:

Rate by which cocaine effectively binds the DAT

↑DA release

↑D2 binding

↑Glutamate neurotransmission

Mice devoid of mGluR5 receptors do not self-administer cocaine

- despite ↑NAc DA levels

Cocaine increases DA and glutamate levels
Euphoria likely requires the activation of both systems

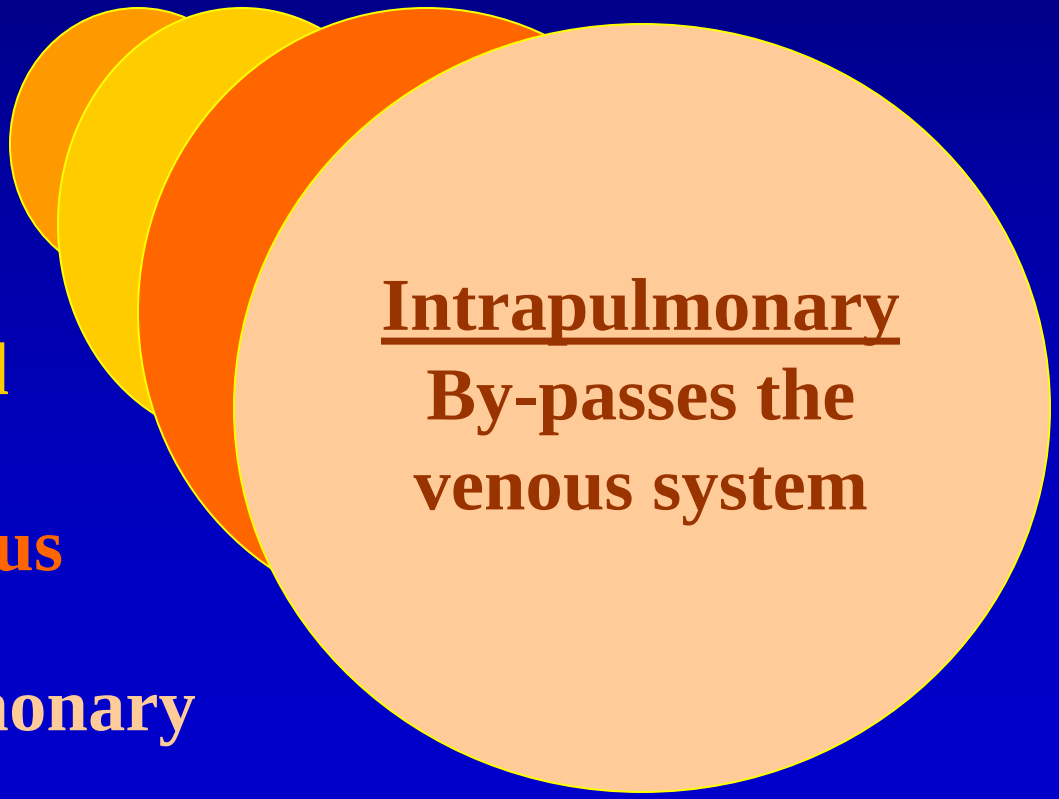
Routes of Administration

Oral

Intranasal

Intravenous

Intrapulmonary



Cocaine Craving

- Cocaine-induced craving
  - Glutamate depletion
- Cue-induced craving
  - DA/glutamate activation
- Stress-induced craving
  - CRF, NE & DA/glutamate activation
- Baseline craving
  - DA/glutamate depletion?

Cocaine-Induced Craving

- Demonstrated under controlled conditions
  - Craving after cocaine exceeds baseline craving
  - Patients feel worse within minutes of cocaine use
- Fuels a characteristic binge use pattern
  - Increases dangerous exposure to the drug
- Glutamate depletion & cocaine-induced reinstatement
  - Cocaine depletes NAc glutamate
  - N-acetylcysteine (normalizes glutamate)
  - N-acetylcysteine obliterates cocaine reinstatement

Glutamate-enhancing drugs may dampen cocaine-induced craving

Cue-Induced Cocaine Craving

- Clinically pernicious - leads directly to relapse
- Persistent (weeks, months, years)
- Compelling
- Often unpredictable
- Difficult to avoid
- Involves reward-related memory (LTP)

Might cue-induced craving respond to pharmacotherapy?

Neuroimaging Studies of Cue Craving

Robust limbic activation (PET & fMRI) - many studies

Amygdala

Glutamatergic frontal regions

Craving intensity correlates with limbic activation

Same regions activated by sexually explicit videos

(Cocaine hijacks sex reward circuits)

Baclofen ($GABA_B$ agonist) may reverse cue craving

Limbic activation provides a means of testing anti-craving medications in the laboratory under controlled conditions

Stress-Induced Cocaine Craving

Patients often relapse during periods of stress

- Traditionally seen as a wish to "escape" via cocaine
- Purely psychological reaction

Biological basis suggested by animal studies

Stress-induced reinstatement

- ↑CRF release
- ↑Norepinephrine release

Might stress-induced craving respond to CRF or norepinephrine antagonists?

Stress-Induced Cocaine Craving

CRF activates reward circuits in cocaine addicted animals

Stress releases CRF in all animals

Stress only releases DA in cocaine treated animals

DA is released via CRF-induced elevation of glutamate in the VTA

DA release is required for stress-induced reinstatement

Agents that block DA and/or glutamate might dampen stress-induced craving

DA/glutamate antagonists (or GABA agonists) might dampen stress-induced craving?

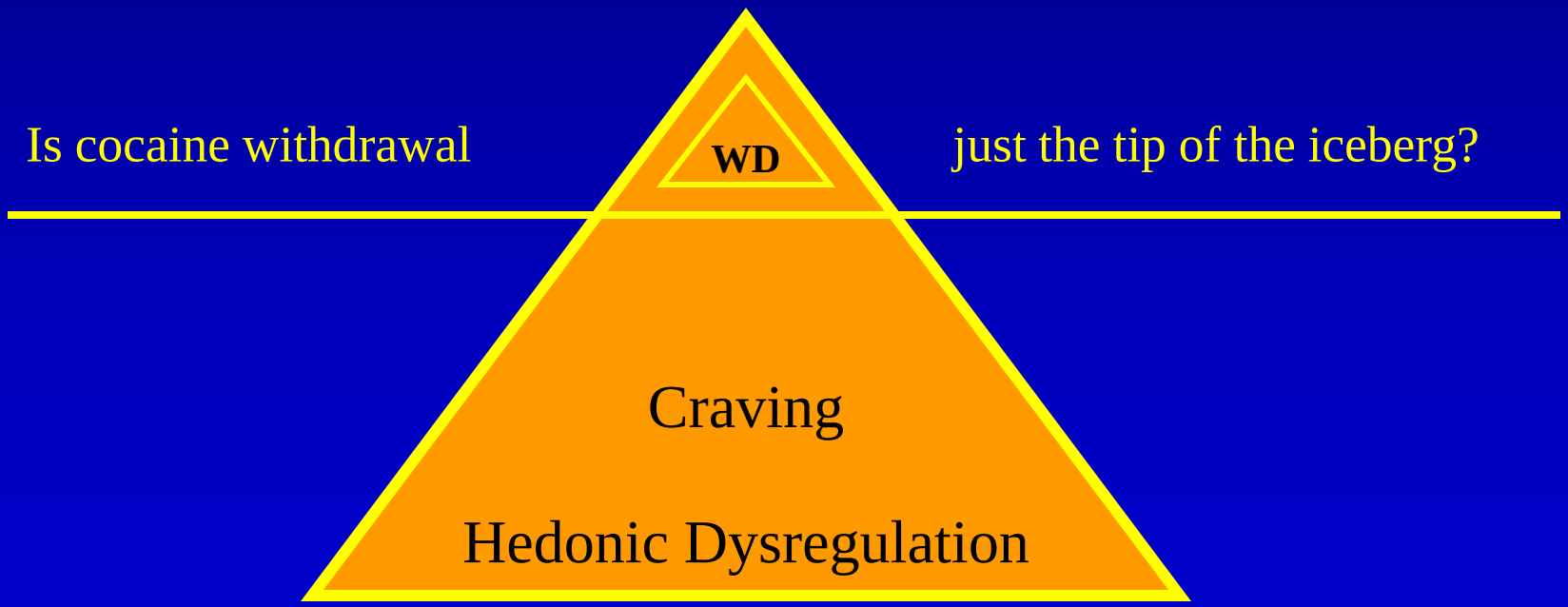
Cocaine Withdrawal

Anergia
Depression
Bradycardia
Hyperphagia
Hypersomnia
Poor concentration
Psychomotor retardation

Cocaine withdrawal is not medically dangerous but severe withdrawal curiously predicts poor clinical outcome

Cocaine WD Predicts Poor Outcome

Several studies report that the presence of severe cocaine withdrawal symptoms at baseline predicts poor clinical outcome



Cocaine-Induced Neuroadaptations

Reversing cocaine-induced neuroadaptations represents another viable pharmacological strategy

Clinical components that may respond include:

Baseline craving, cocaine withdrawal, hedonic dysregulation, and even denial . . .

Principle cocaine-induced neuroadaptations include:

DA depletion

Glutamate depletion

GABA/dynorphin upregulation

A role for DA/glutamate agonists or GABA/dynorphin antagonists

Glutamate Dysregulation by Cocaine

Reduced NAc glutamate levels

(Keyes 1998, Bell 2000, Hotsenpiller 2001,Kalivas 2005)

Reduced NAc Glu synaptic strength

(Swanson 2001, Thomas 2001)

Downregulated mGluR2/3 autoreceptors (compensatory response?) (Xi 2002)

Cocaine acutely increases but chronically inhibits glutamate activity

Dopamine Dysregulation by Cocaine

Cocaine-Addicted Patients

Reduced presynaptic DA activity (PET)

6-Fluorodopa (Wu 1997), Raclopride (Volkow 1997)

Reduced [DA] at autopsy (Wilson 1996, Little 1996, 1999)

Reduced D2 availability (Volkow 1999)

Hyperprolactinemia

(Dackis 1985, Mendelson 1988, Lee 1990, Teoh 1990*
Satel 1991, Vescovi 1992, Kranzler 1992*, Elangovan 1996
Patkar 2002*) *Associated with poor clinical outcome

↓DA tone on electroretinography (Roy 1997, Smelson 1998)

Cocaine acutely increases but chronically inhibits DA activity

DA-Enhancing Agents for Cocaine Dependence

Two recent controlled studies reported efficacy in cocaine dependence with DA-enhancing agents:

Modafinil (400 mg/day; n = 62) (Dackis et al, 2005)

- Enhances DA through DAT blockade

Disulfiram (250 mg/day; n = 121) (Carroll et a; 2004)

- Enhances DA by inhibiting dopamine β-hydroxylase

Conversely, the DA antagonist olanzapine destabilized cocaine-dependent subjects (Kampman 2003)

Functions Ascribed to Prefrontal Cortex

- Decision-making
- Weighing of risks vs. rewards
- Assigning emotional valence to stimuli
- Suppressing limbic impulses
- Goal-directed behaviors

*Might PFC dysfunction contribute to **denial**?*
Is there a role for agents that increase PFC activity?

Denial: The Hallmark of Cocaine Dependence

- Poor decision making
- Impaired ability to weigh risks against benefits
- Dangerous risk tolerance
- Poor impulse suppression
- Cocaine becomes the first priority

Denial, traditionally viewed as purely psychological, may result in part from prefrontal cortical dysfunction

Natural History - Relapse and Progression

- Increased dose and frequency
- Change of route of administration
- Development of tolerance
- Development of withdrawal symptoms
- Medical and psychiatric complications
- Functional impairment

Progressive Complications of Cocaine Dependence

- **Death** (MI, hyperthermia, hemorrhage, violence)
- **Medical** (cardiac, seizures, stroke, renal)
- **Psychiatric** (psychosis, depression, panic, suicide)
- **Legal** (incarceration: possession, dealing, prostitution, theft)
- **Family** (child neglect, violence, divorce)
- **Occupational** (job loss: absenteeism, poor performance)
- **Financial** (drug procurement, loss of income)

Denial shields patients from their predicament

Treatment of Stimulant Dependence

- Provider requires specialized knowledge
- Patient requires motivation
  - Patient may not want to stop using drugs
  - Attitude/Compliance is important
- Recovery requires sacrifice
- Clinical course involves relapse/progression

Assessment & Treatment

- Comprehensive Assessment
  - Medical
  - Psychiatric
  - Psychiatric
  - Psychosocial
- Abstinence Initiation
  - Readiness for change
- Relapse Prevention
  - Different levels of care
  - Inpatient, IOP, outpatient

Importance of Collateral Information

"Substance abusers are reluctant to disclose sensitive personal information"

(They lie)

Sources of Collateral Information

Laboratory Testing

Physical Examination

Family\Informant Interviews

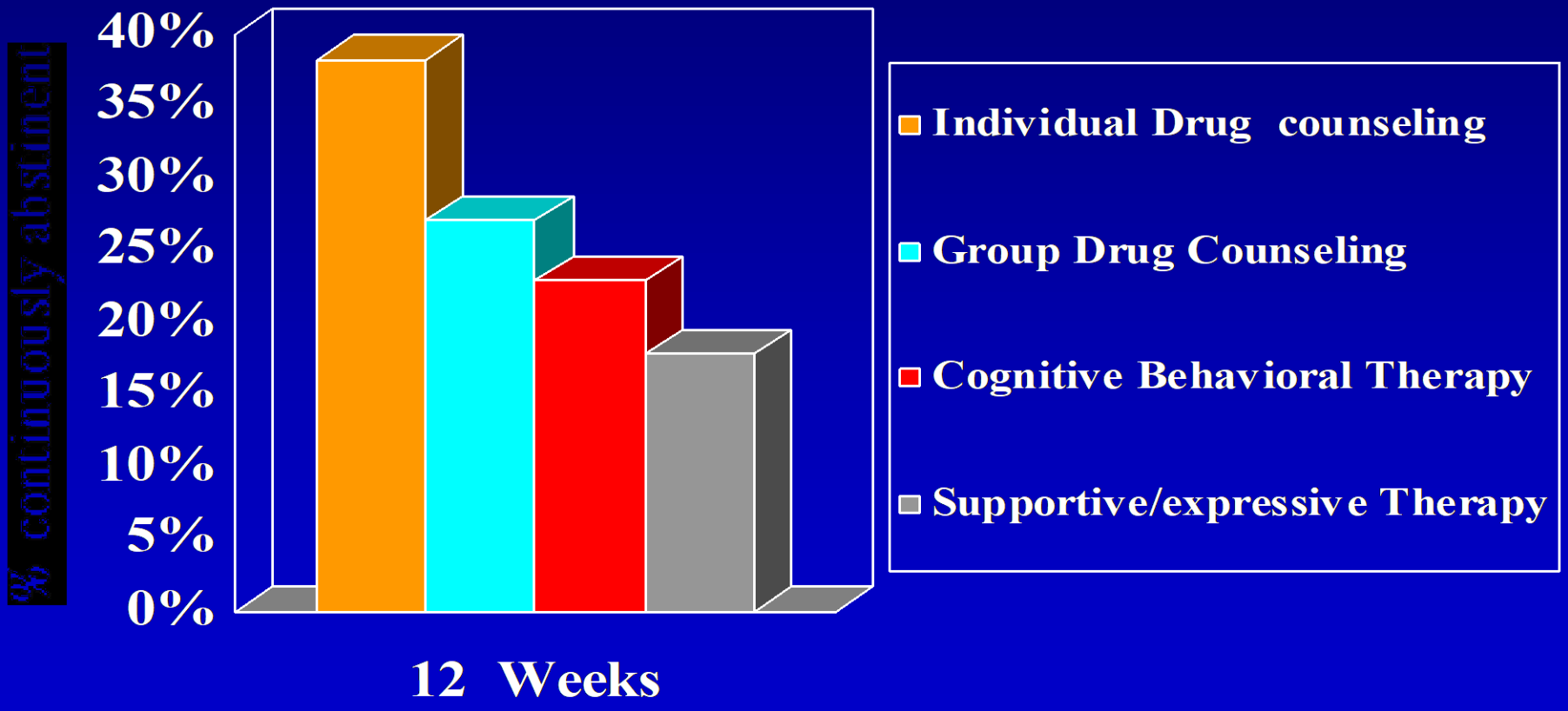
Past Medical Records

Treatment Modalities

- Intervention
- Abstinence-based AA/NA model
- Individual, group, & family therapy
- Pharmacotherapy

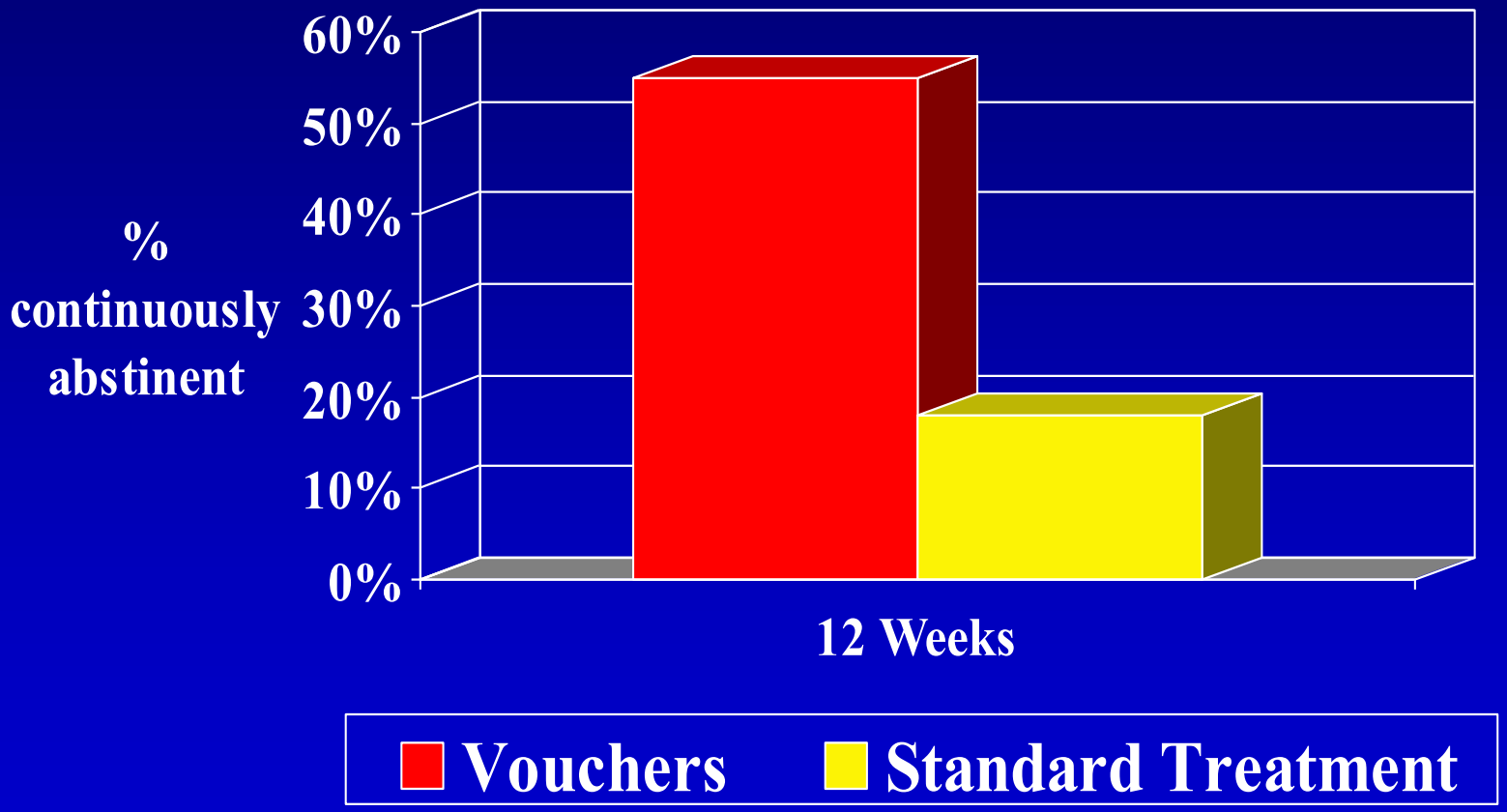
Treatment of cocaine dependence - Psychosocial

Individual drug counseling is effective



Treatment of cocaine dependence - Psychosocial

Voucher treatment improves short-term abstinence



(Higgins, 1994)

Treatment of Stimulant Dependence - Medications

There are no medications with proven efficacy for stimulant dependence

Treatment of cocaine dependence - Medications

- Possible medications include:
  - Modafinil - blocks euphoria
  - Propranolol - reduces stress
  - Baclofen - reduces cue-craving
  - Topiramate - relapse prevention
  - Disulfiram - reduces alcohol use, increases DA
  - Cocaine vaccine - blocks euphoria

Distinct Clinical Components of Cocaine Dependence

Cocaine Euphoria

Cocaine-Induced Craving

Cue-Induced Craving

Stress-Induced Craving

Baseline Craving

Cocaine Withdrawal

Hedonic Dysregulation

Hypofrontality

These clinical components occur at different time points and could be targeted by specific pharmacotherapies

It is very unlikely that a single medication could treat each of these clinical phenomena

Conceptualizing Pharmacotherapy

Abstinence Initiation

DA/Glutamate Enhancing Agents

- Modafinil (glutamate-enhancing)*
- Amantadine (releases DA)*
- Disulfiram (↑brain DA; ↓DBH)*

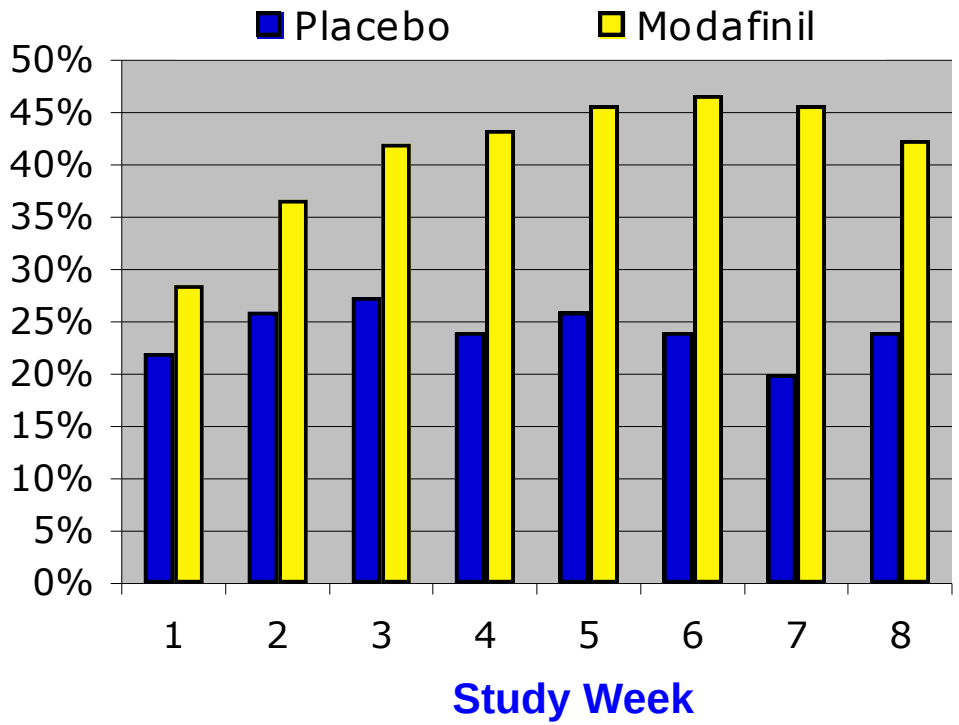
DA/Glutamate Inhibiting Agents

- Ondansetron (↓DA release)
- Tiagabine (↓GABA uptake)
- Baclofen ($GABA_B$ agonist)*
- Topiramate (↑GABA, AMPA blocker)*

Relapse Prevention
(↓Cue Craving)

**Positive findings in DB trials*

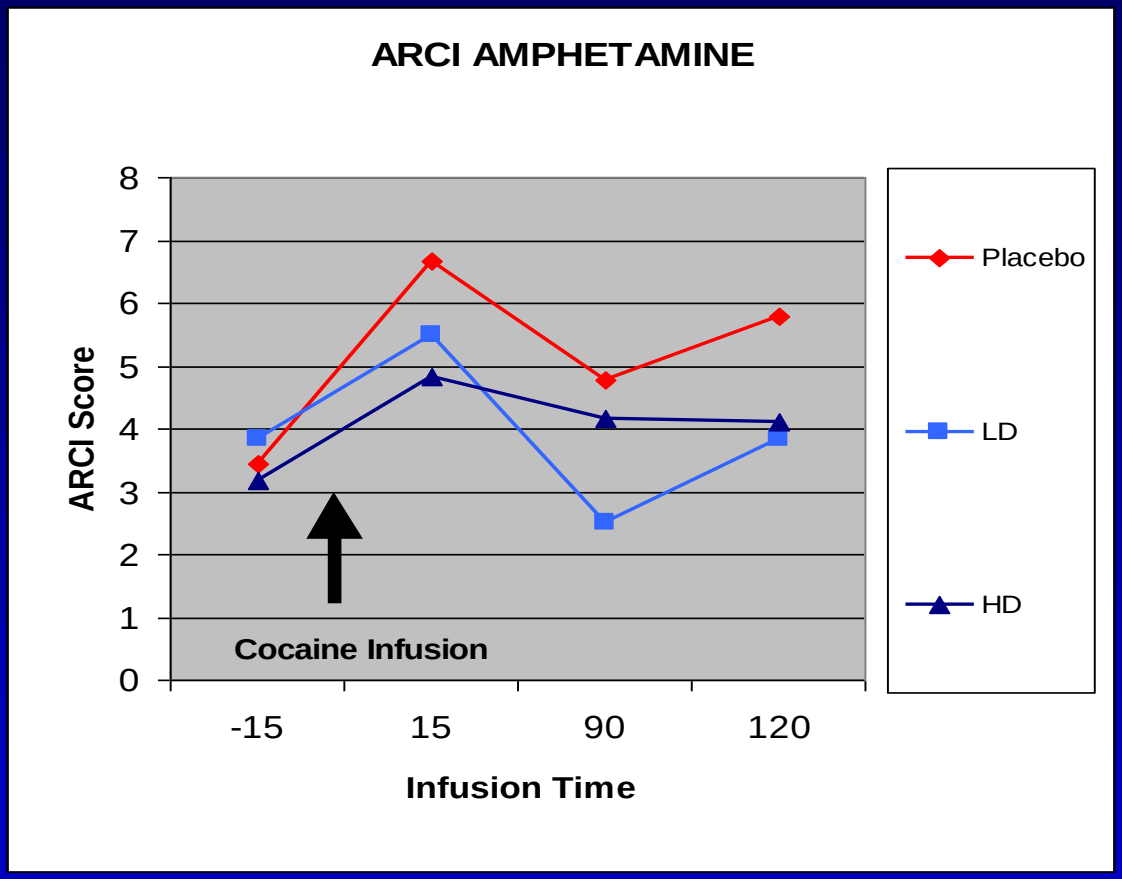
Modafinil Promotes Cocaine Abstinence



Longitudinal GEE models showed a significant main effect for cocaine abstinence in the modafinil group (odds ratio = 2.41, 95% CI 1.09-5.31, p = 0.03)

Dackis et al.***Neuropsychopharmacology,*** 2005

Modafinil Attenuates Cocaine Euphoria

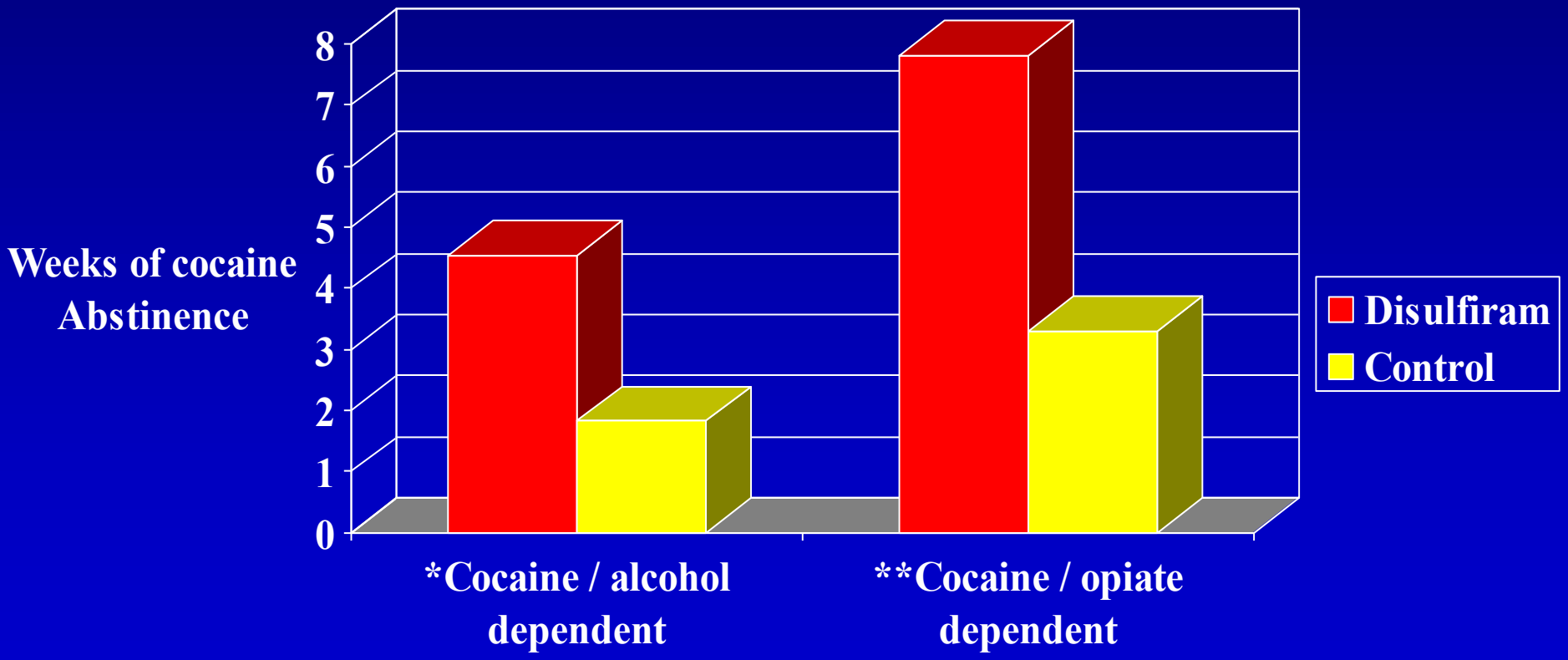


Modafinil (4 days: LD = 200 mg/day, HD = 400 mg/day) reduced euphoria ratings after IV cocaine (p = 0.02)

Dackis et al: Drug and Alcohol Dependence, 2003

Treatment of Cocaine Dependence - Medications

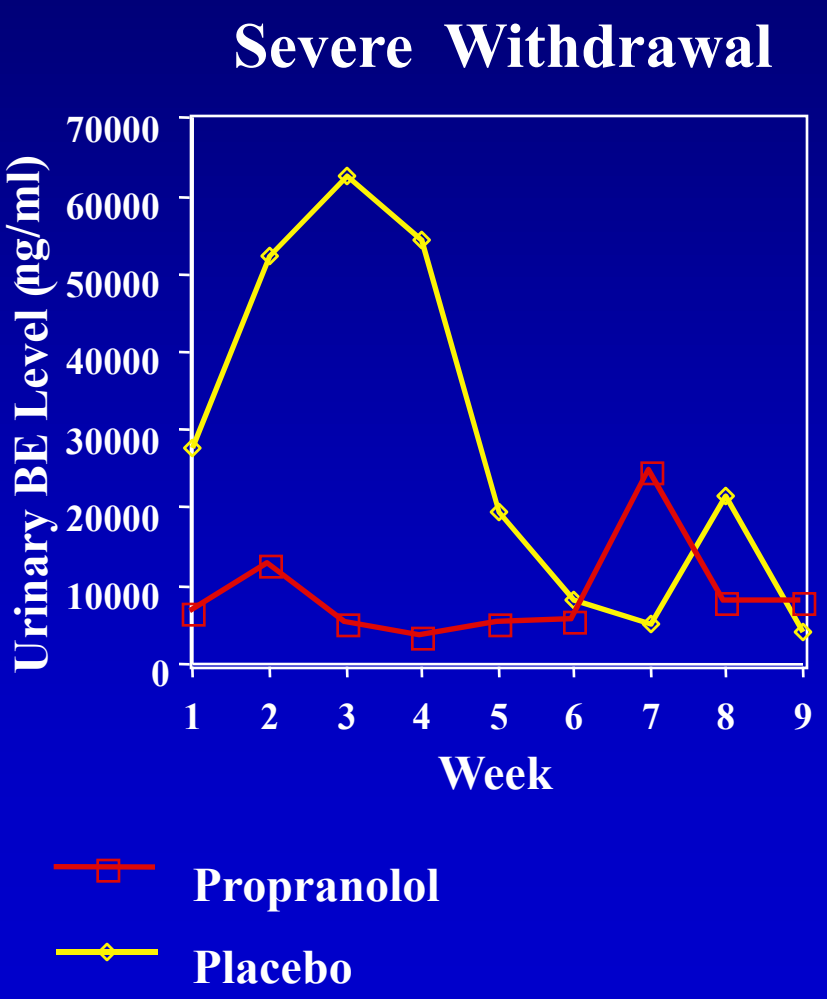
Disulfiram is Effective in Cocaine Dependent Patients With and Without Alcohol Dependence

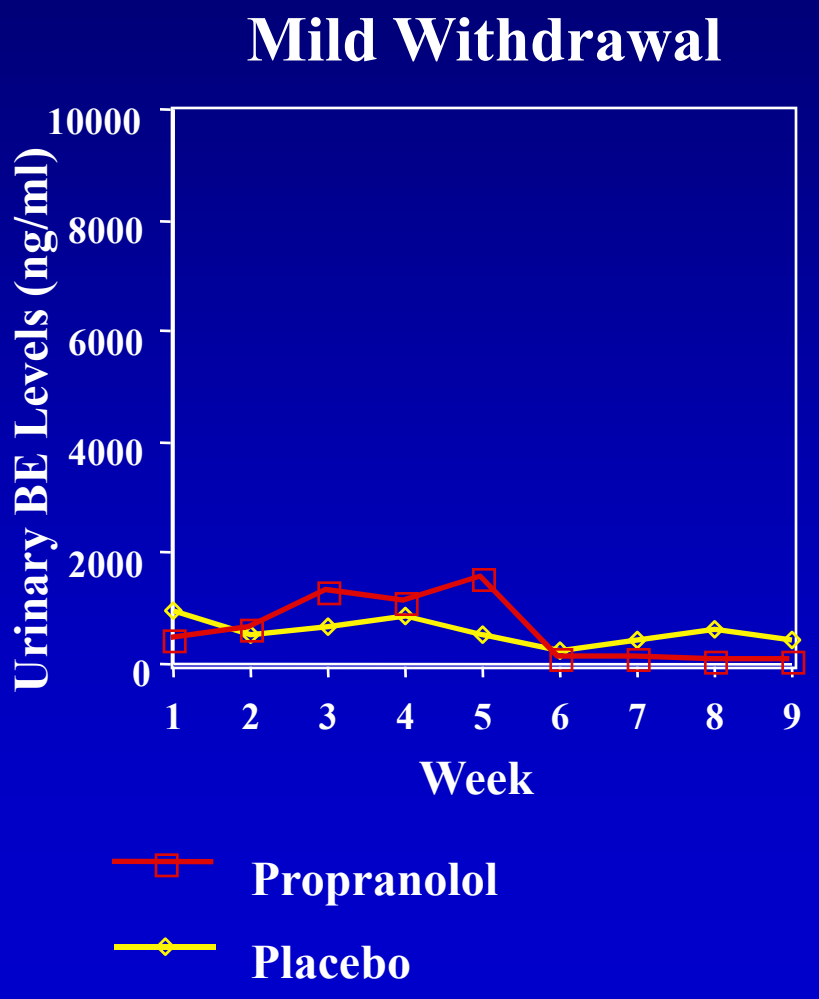


(*Carroll, 1998, ** George, 1999)

Treatment of cocaine dependence - Medications

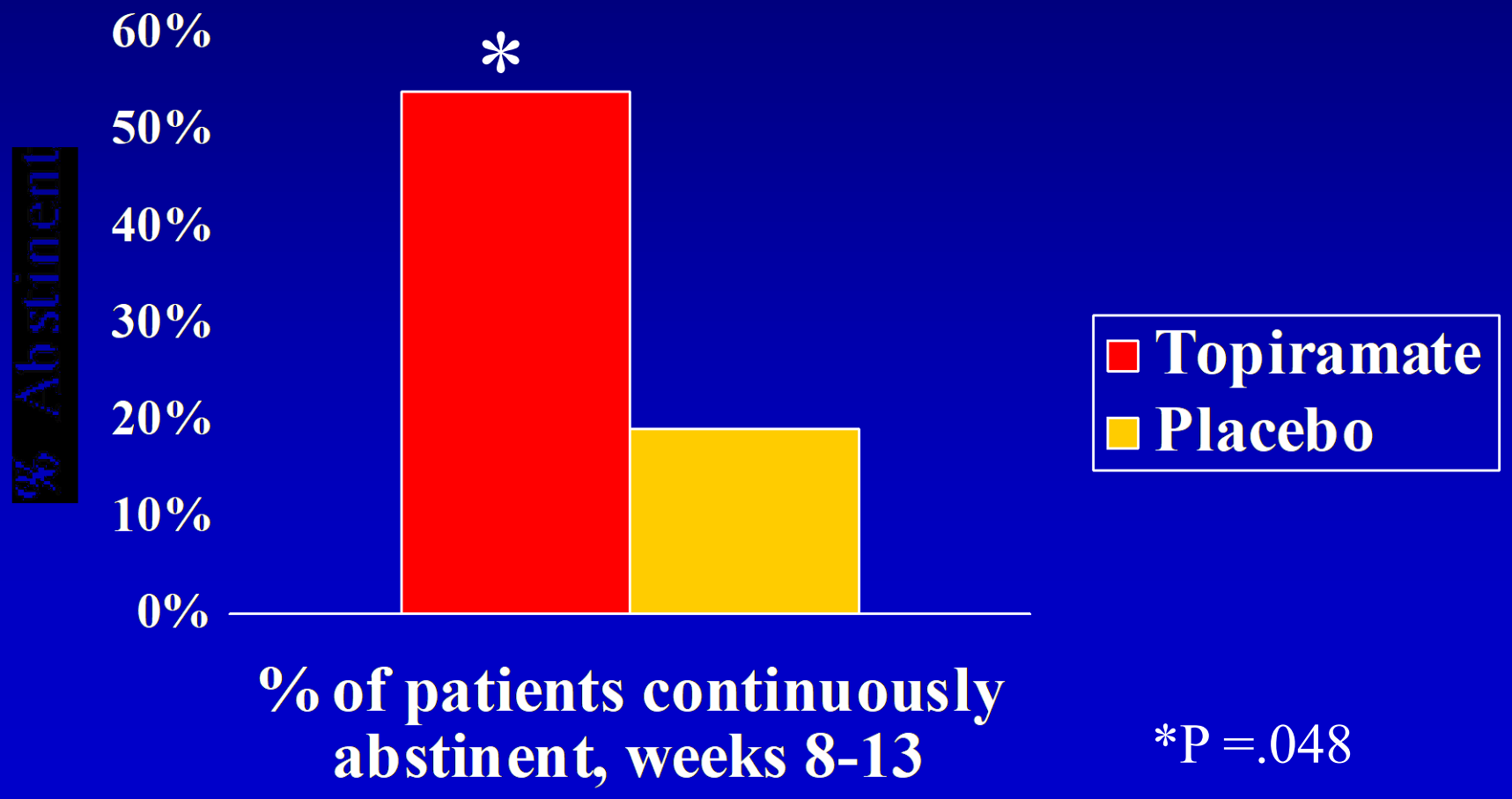
Propranolol reduces cocaine use





Cocaine withdrawal predicts medication outcome

Topiramate Prevents Relapse



*P =.048

Clinical Components of Cocaine Dependence

- **Cocaine-Induced Euphoria**
- **Cocaine-Induced Craving**
- **Cocaine Withdrawal**
- **Cue-Induced Craving**
- **Stress-Induced Craving**
- **Hedonic Dysregulation**
- **Hypofrontality**

These clinical components occur at different time points, and can be targeted by pharmacotherapy.

Patients should be assessed to determine which are most clinically significant

- *GABA Enhancers*
- *DA/Glutamate Enhancers*
- *Cocaine Vaccine*
- *β-Blockers, CRF antagonists?*

Conclusions

- Stimulants like cocaine acutely activate but chronically dysregulate brain reward centers
- The addiction is primarily driving by euphoria and craving
- Stimulant-addicted patients are intrinsically out of control
- Brain neuroadaptations contribute to cocaine euphoria, cue-induced craving, hedonic dysregulation, and even denial
- The initiation of abstinence and relapse prevention require specialized treatment
- Medication development may significantly improve the prognosis of this chronic, relapsing disorder

Post-Lecture Exam Question 1

1. Which of the following is not known as a stimulant?

a. Methamphetamine

b. Buproprion

c. Methylphenidate

d. Lamphetamine

Post-Lecture Exam Question 2

2. Which form of cocaine administration is the most effective route of administration?

a. Oral

b. Intrapulmonary (inhalation)

c. Intranasal

d. Subcutaneous

Post-Lecture Exam Question 3

3. The cocaine withdrawal syndrome consists of which of the following?

a. Anergia
b. Mood depression
c. Hypersomnia
d. Nausea
e. None of the above
f. a, b, and c

Post-Lecture Exam
Question 4

4. There is no evidence from controlled trials that the following medication is useful in enhancing cocaine abstinence:

a. Topiramate

b. Paroxetine

c. Disulfram

d. Modafinil

Post-Lecture Exam Question 5

5. Previously, and to this day, cocaine has been used legally for medicinal and recreational purposes. Which statement is true?

a. Chewing coca leaves is highly addictive and is a major health problem in South America.

b. Coca Cola originally contained 100 mg of cocaine per bottle.

c. Cocaine wine was used primarily to induce sleep.

d. Cocaine has analgesic properties.

Answers to Pre and Post Lecture Exams

1. B
2. B
3. F
4. B
5. D