

Stimulants

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Pre-Lecture Exam

Question 1

1. Which of the following is not known as a stimulant?
 - a. Methamphetamine
 - b. Bupropion
 - 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. Disulfiram
 - 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

Revised Retail Prices of

COCA WINE.

ARMBRECHT'S
FOR FATIGUE OF MIND AND BODY.
And Consequent Affections, as
**NEURALGIA,
SLEEPLESSNESS,
DESPONDENCY,**
AND ALL THE AFFECTIONS OF THE NERVOUS SYSTEM.



TWELVE BOTTLES, 48s. TWENTY-FOUR BOTTLES, 94s.
Carriage Paid to any Port, and Duty for United Kingdom. Free of Duty on Importation.

Professional Prices: 40s. per dozen; 21s. half-dozen.
Carriage Paid on each.

ARMBRECHT, NELSON & CO.,
Temporary Agents: 2, Duke St., Grosvenor Square, London, W.
Wholesale and Retail: "ARMBRECHT, NELSON & CO., LONDON."

A Sample Bottle free to Special Res. and Dispens. on receipt of professional card.

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.



MARIANI WINE

MARIANI WINE Quickly restores
**HEALTH, STRENGTH,
ENERGY & VITALITY.**

MARIANI WINE
FORTIFIES, STRENGTHENS,
STIMULATES & REFRESHES
THE BODY & BRAIN

HASTENS
CONVALESCENCE
especially after
INFLUENZA.

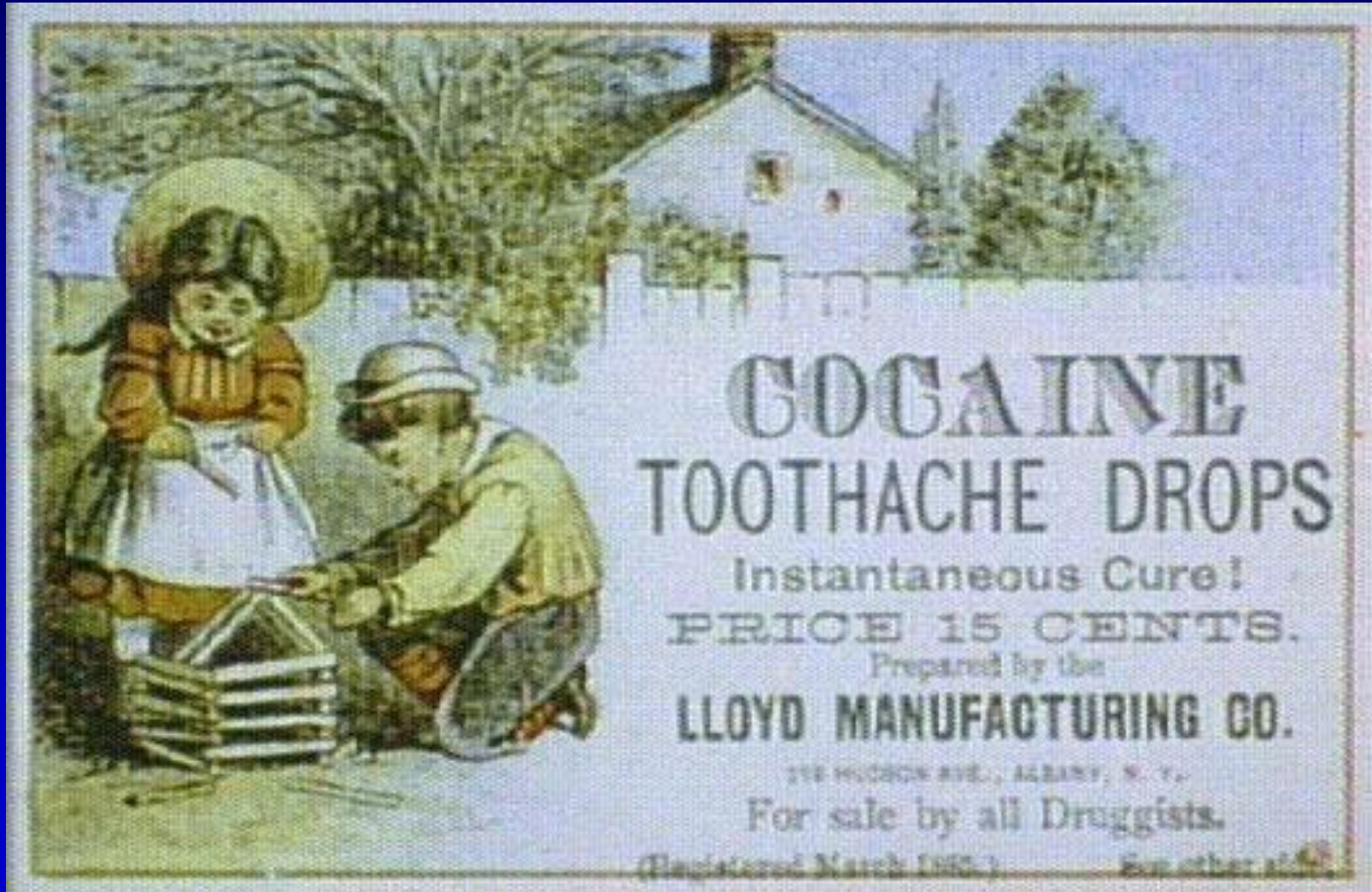
His Holiness
THE POPE

writes that he has fully appreciated the beneficent effects of this Tonic Wine and has forwarded to Mr. Mariani as a token of his gratitude a gold medal bearing his august effigy.

MARIANI WINE

Is delivered free to all parts of the United Kingdom by WILCOX & CO.,
83, Mortimer Street, London, W., price 4/- per Single Bottle, 22 0 half
dozen, 45/- dozen, and is sold by Chemists and Stores.

Cocaine History



COCAINE
TOOTHACHE DROPS
Instantaneous Cure!
PRICE 15 CENTS.
Prepared by the
LLOYD MANUFACTURING CO.
178 HICKORY AVE., ALBANY, N. Y.
For sale by all Druggists.
(Registered March 1885.)

The illustration shows a woman in a yellow dress and hat kneeling to help a young child in a white dress and orange vest. They are outdoors in front of a white house with a chimney. The child is holding a small basket.

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.

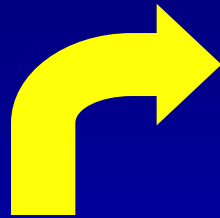
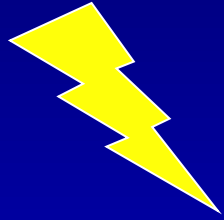
Education can address perceived risk but law enforcement efforts to limit supply have not been particularly successful

Cycle of Cocaine Addiction

This addiction has biological, behavioral & psychological aspects

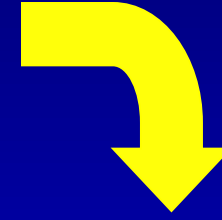
Cocaine

Use



EUPHORIA

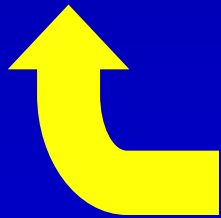
Positive Reinforcement



Brain Reward

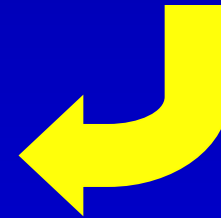
Neuroadaptations

Cocaine
Seeking
Behavior



CRAVING

Negative Reinforcement

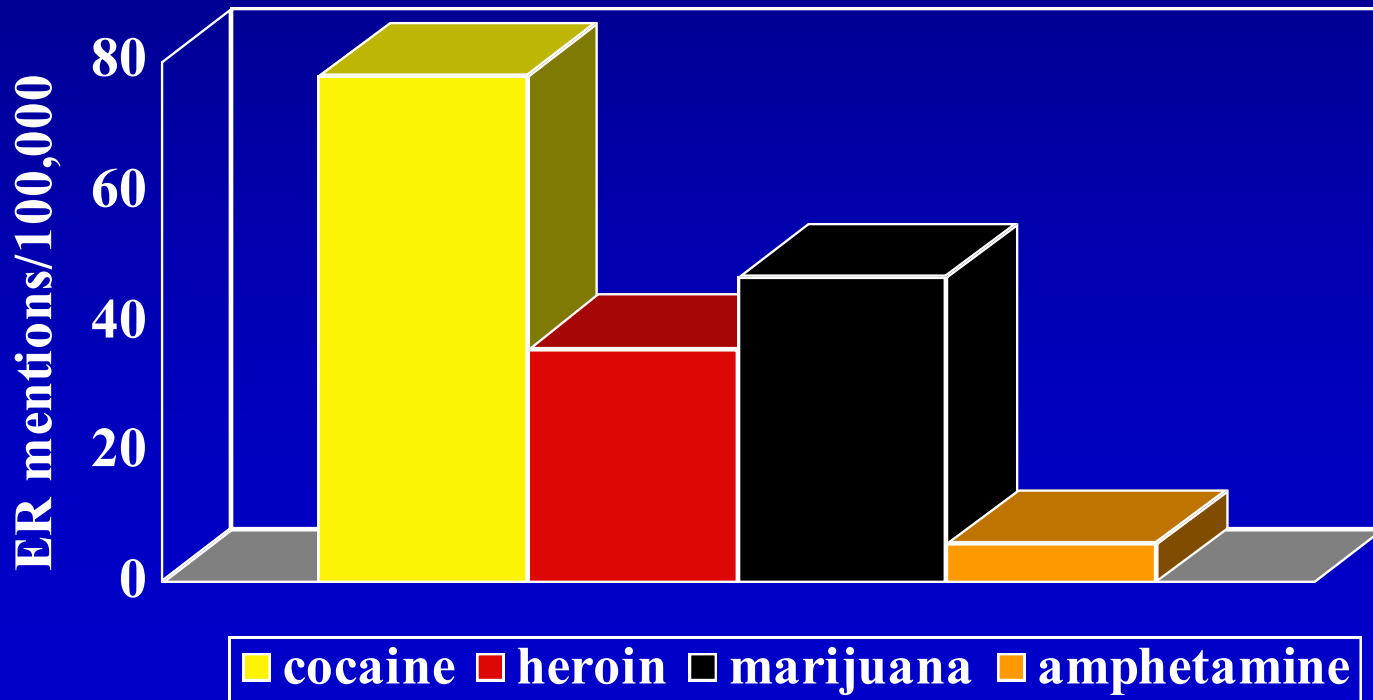


Treatment interventions are designed to reduce euphoria & craving

Toxicity

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

Drug Abuse Warning Network Survey



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

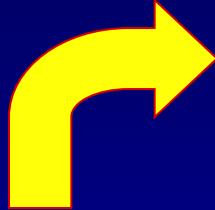
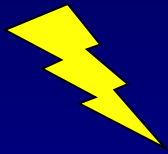
Hypofrontality

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

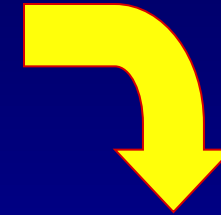
Dynamic Cycle of Cocaine Addiction

Cocaine



+

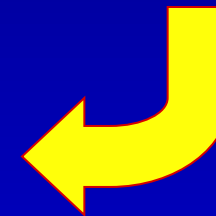
Cocaine Euphoria
Positive Reinforcement
Activated Reward Pathways
↑DA/Glutamate



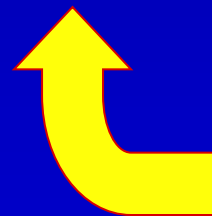
Reward Dysregulation
Cocaine Withdrawal
↓DA/Glutamate
↑Dynorphin/GABA

-

Cocaine Craving
Negative Reinforcement
↓DA/Glutamate

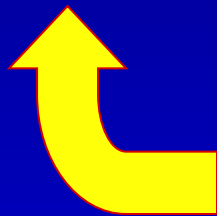


Cocaine Cues
Limbic Activation
↑DA/Glutamate



Stress

Cocaine Administration
Drug-Seeking Behavior
Failed Impulse Suppression
Multiple Risks/Hazards



Loss of Control
Denial / Poor Decision-Making
Hypofrontality / Low D2
Reduced Gray Matter Density

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

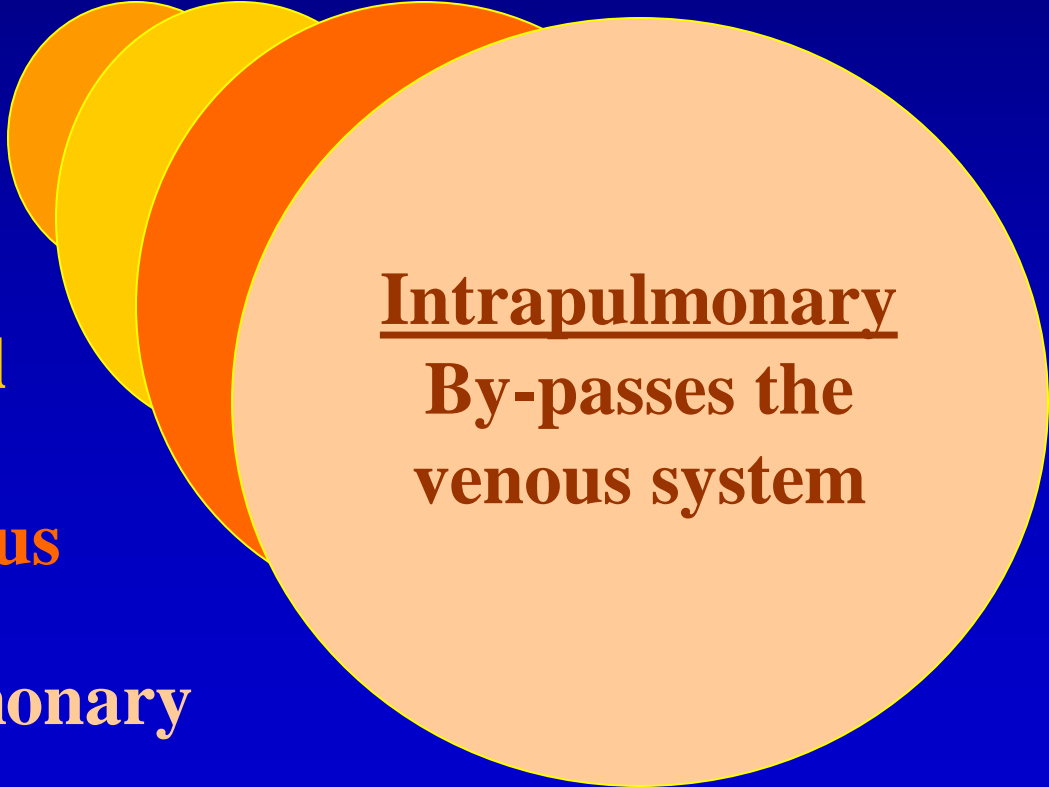
Routes of Administration

Oral

Intranasal

Intravenous

Intrapulmonary



Intrapulmonary
**By-passes the
venous system**

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

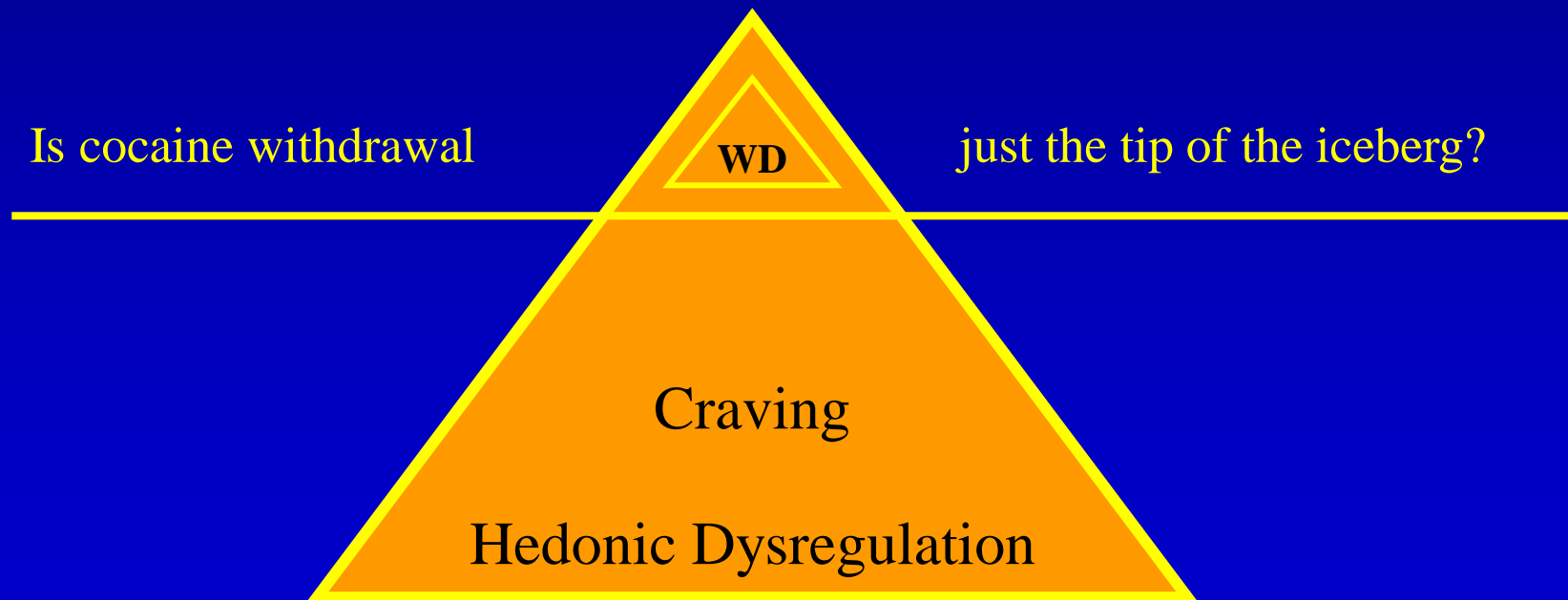
Poor concentration

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 al; 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

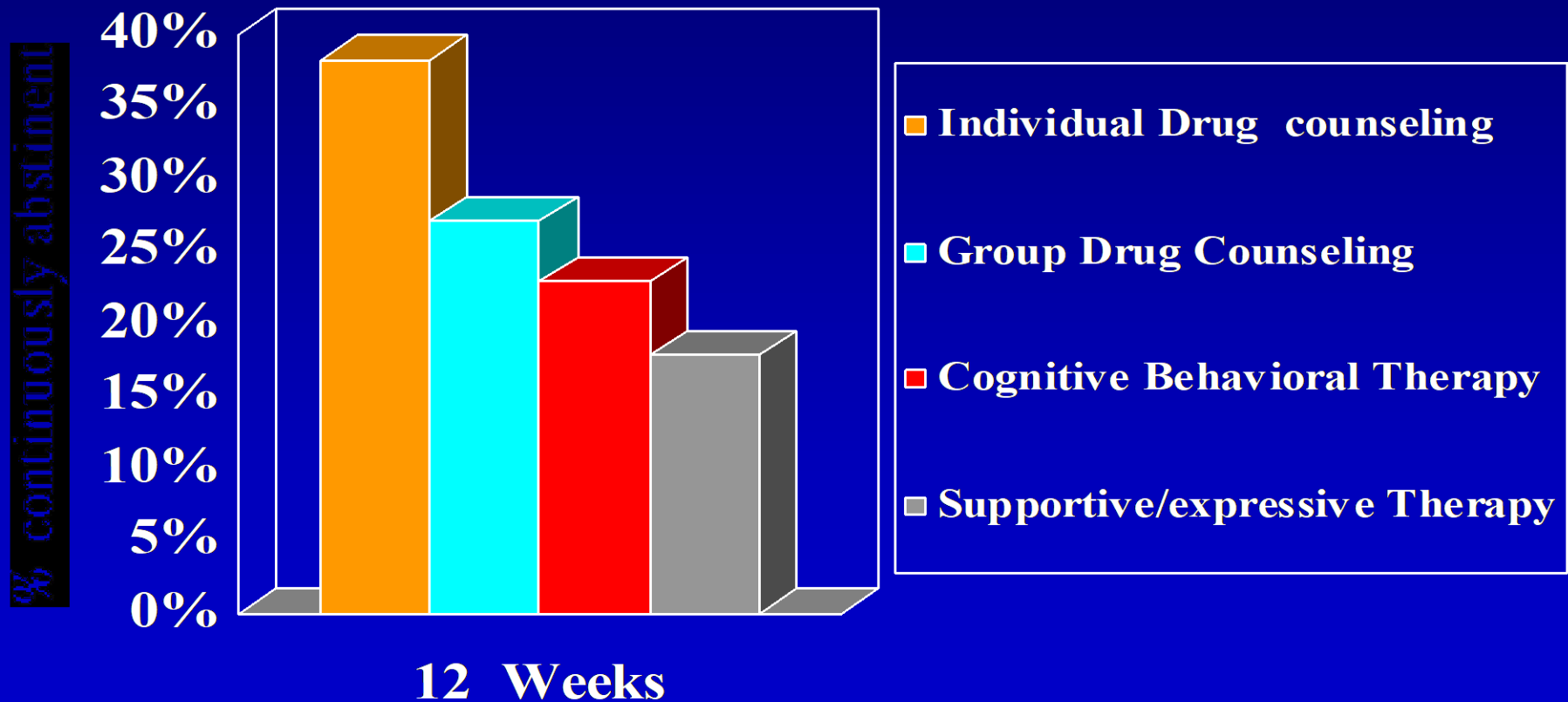
Past Medical Records

Treatment Modalities

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

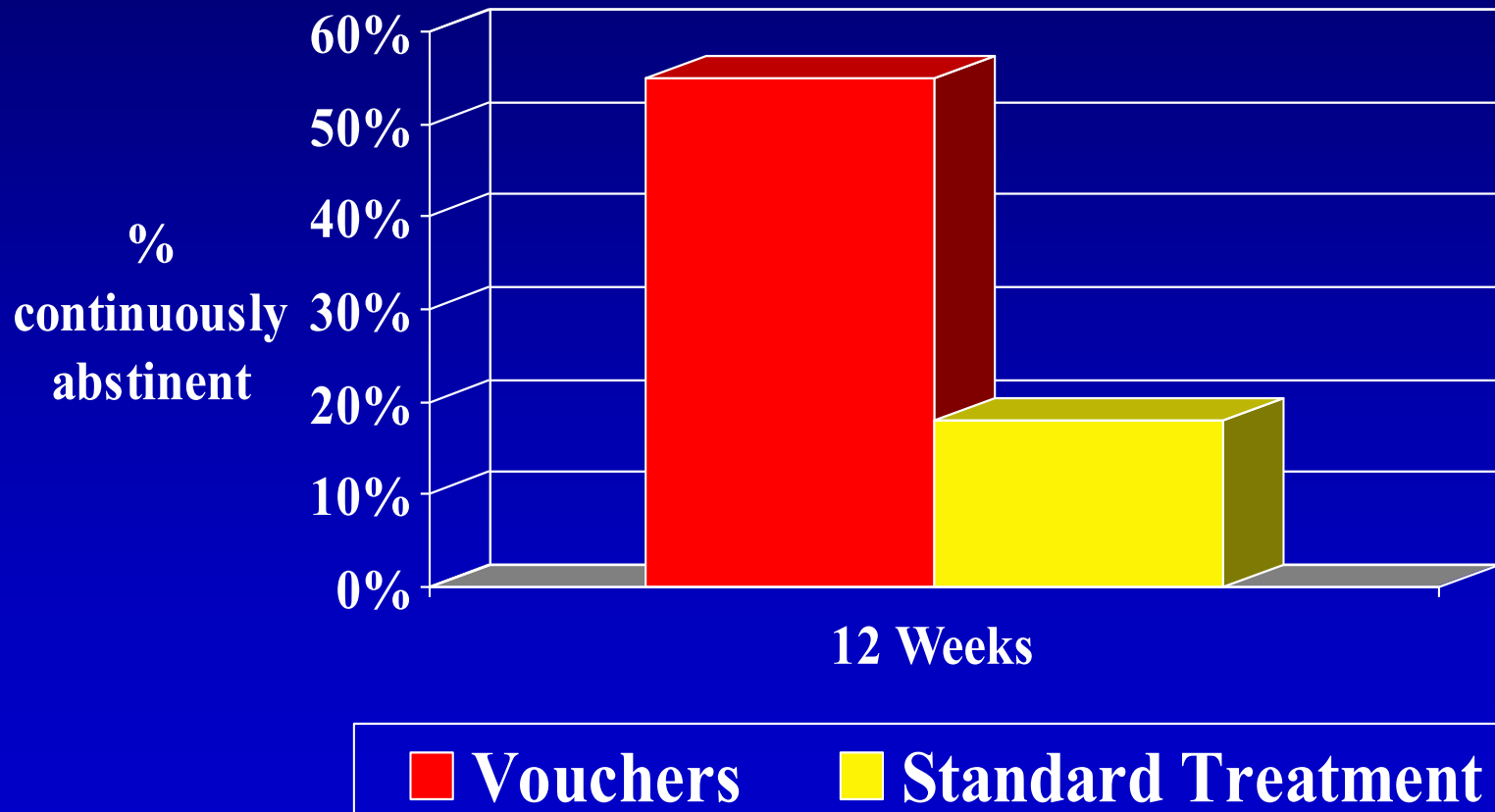
Treatment of cocaine dependence - Psychosocial

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)*

Relapse
Prevention
(↓Cue Craving)

DA/Glutamate Inhibiting Agents

Ondansetron (↓DA release)

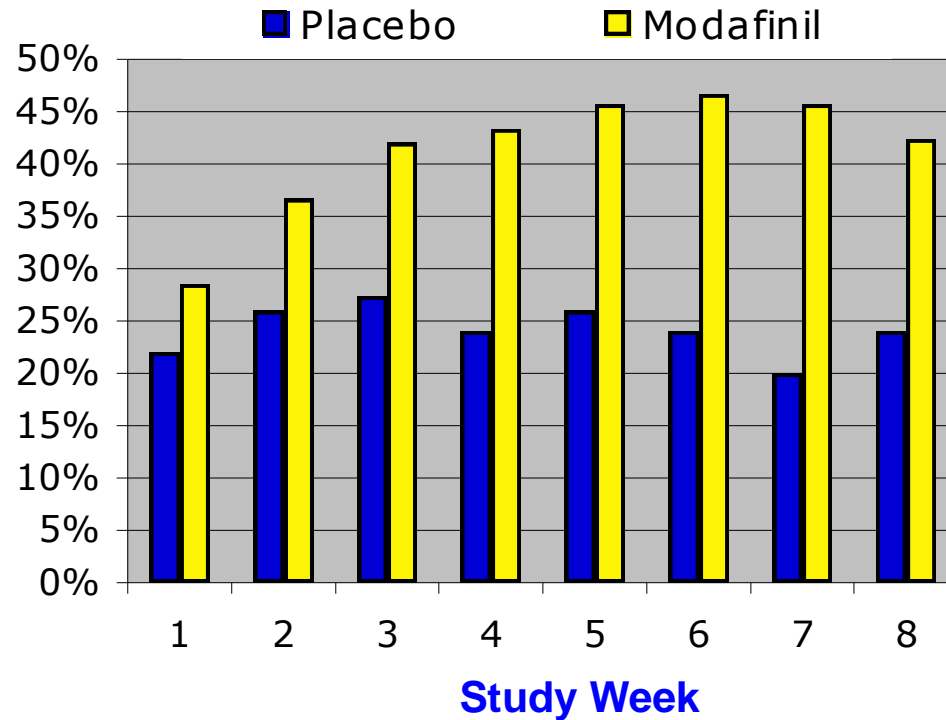
Tiagabine (↓GABA uptake)

Baclofen (GABA_B agonist)*

Topiramate (↑GABA, AMPA blocker)*

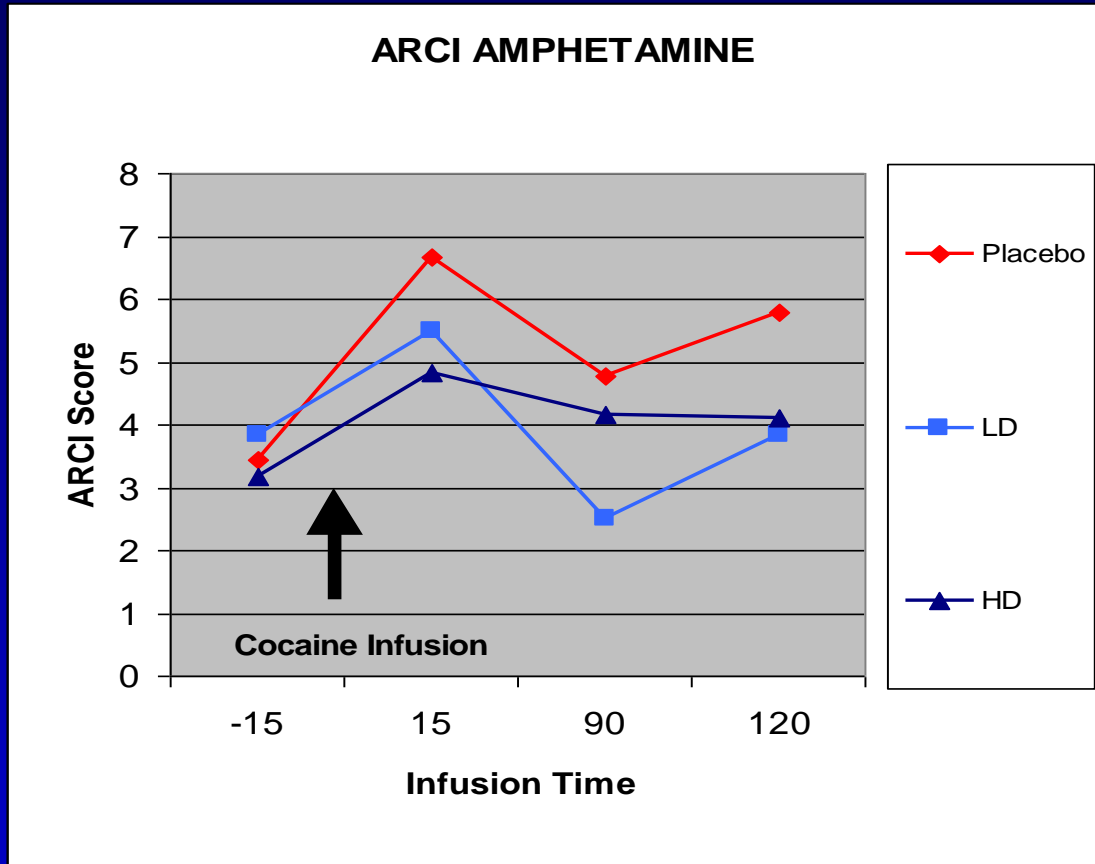
**Positive findings in DB trials*

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, $p = 0.03$)

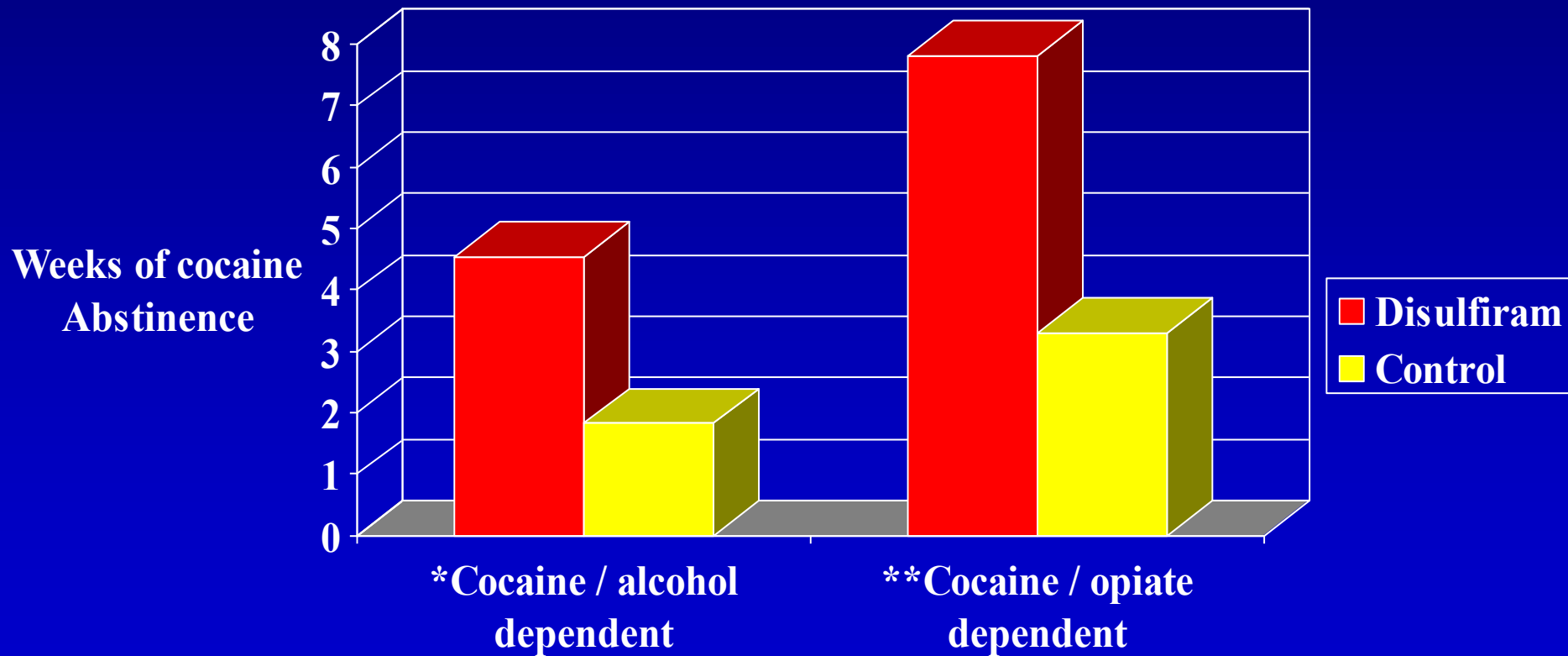
Modafinil Attenuates Cocaine Euphoria



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

Treatment of Cocaine Dependence - Medications

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

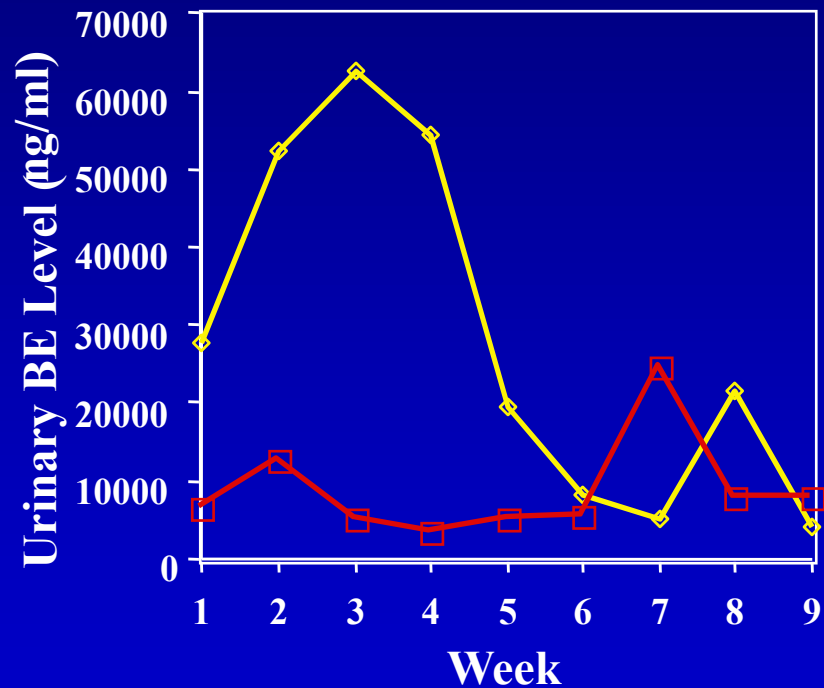


(*Carroll, 1998, ** George, 1999)

Treatment of cocaine dependence - Medications

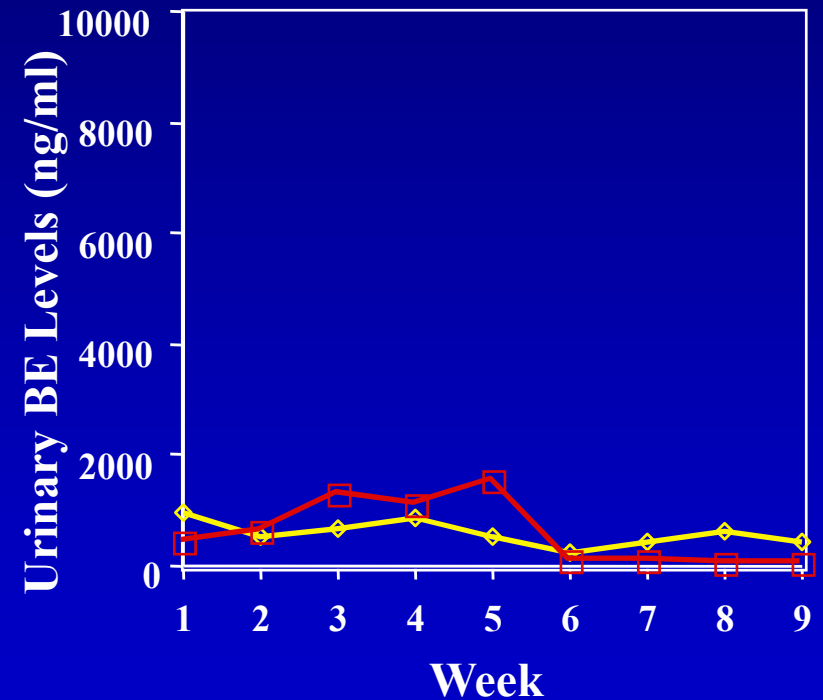
Propranolol reduces cocaine use

Severe Withdrawal



—□— Propranolol
—◇— Placebo

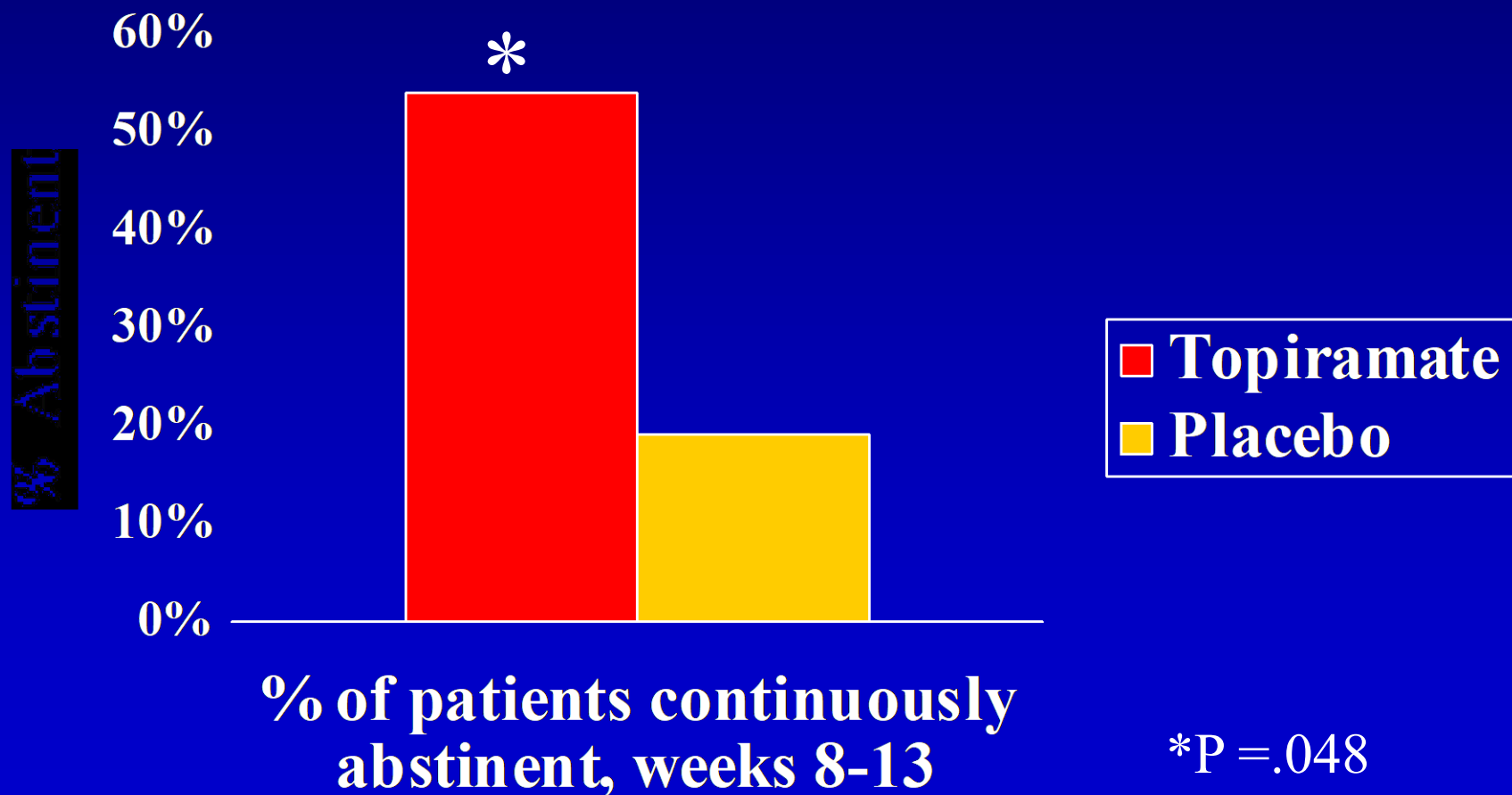
Mild Withdrawal



—□— Propranolol
—◇— Placebo

Cocaine withdrawal predicts medication outcome

Topiramate Prevents Relapse



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

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 - 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
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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. Disulfiram
 - 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