

Medications For The Treatment Of Opiate Dependence In The US

Current Therapies And New Developments

WHO Meeting

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ON DRUG ABUSE

Current Therapies

- Methadone
- LAAM
- Buprenorphine
- Naltrexone
- Lofexidine (in some countries)

Current Needs

Greater availability of treatment

Medications for special populations

Non-opiate medications for opiate dependence

Medications to Treat Withdrawal

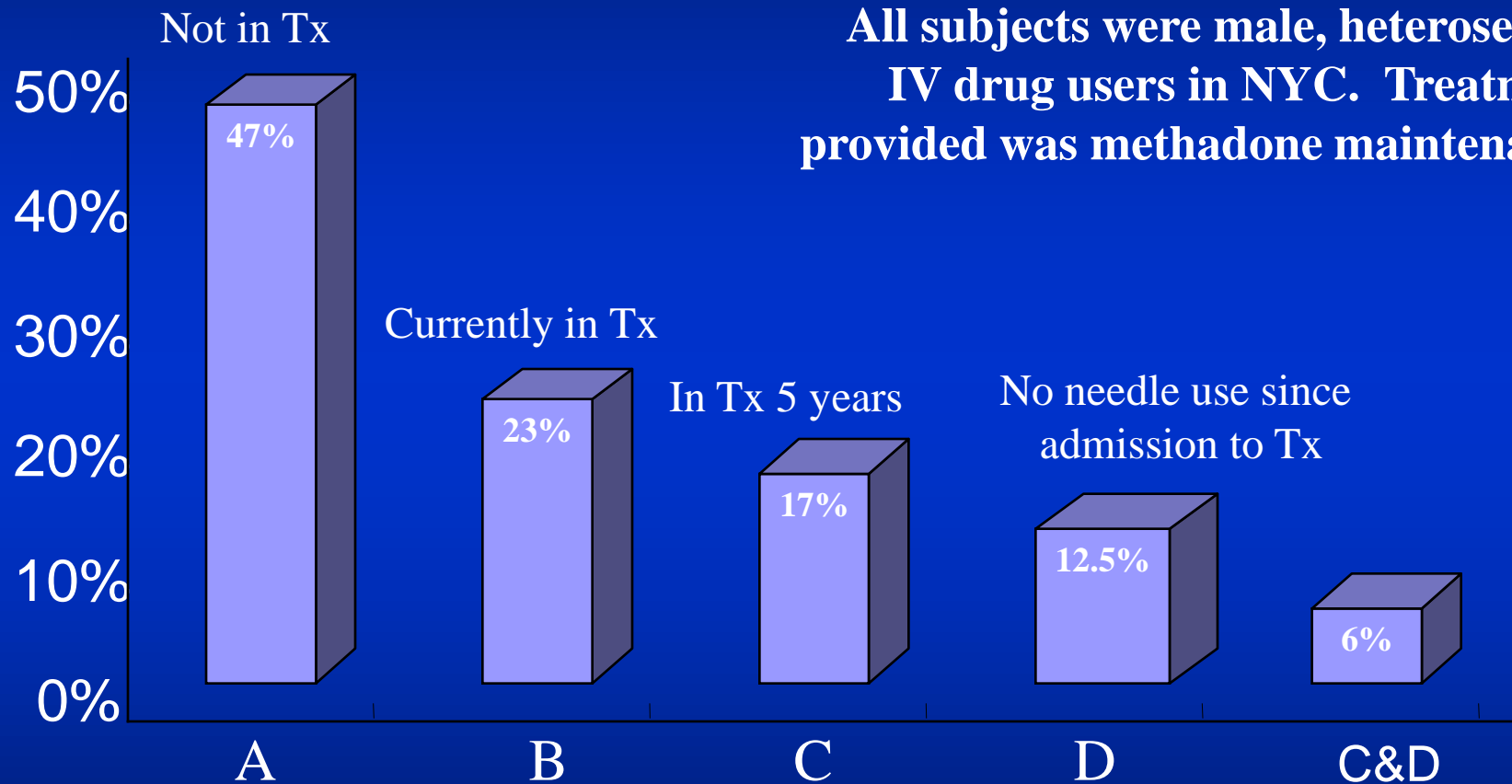
Medications to Treat Relapse

METHADONE

MM and Addicts' Risk of Fatal Heroin Overdose

Authors	Country	# of Ss	Comparison Groups	RR
Gearing, 1974	USA	14,474 1,170	Maint/ Discharged	0.27
Cushman, 1977	USA	1,623 291	Maint/ Discharged	0.32
Gunne, 1981	Sweden	34/32	MM/No MM	0
Gronbladh, 1990	Sweden	1,143 1,406	MM/ Discharged	0.25
Poser, 1995	Germany	149/167	MM/Heroin	0.22

The Effect of Methadone Treatments on HIV Seropositivity Rates



All subjects were male, heterosexual IV drug users in NYC. Treatment provided was methadone maintenance.

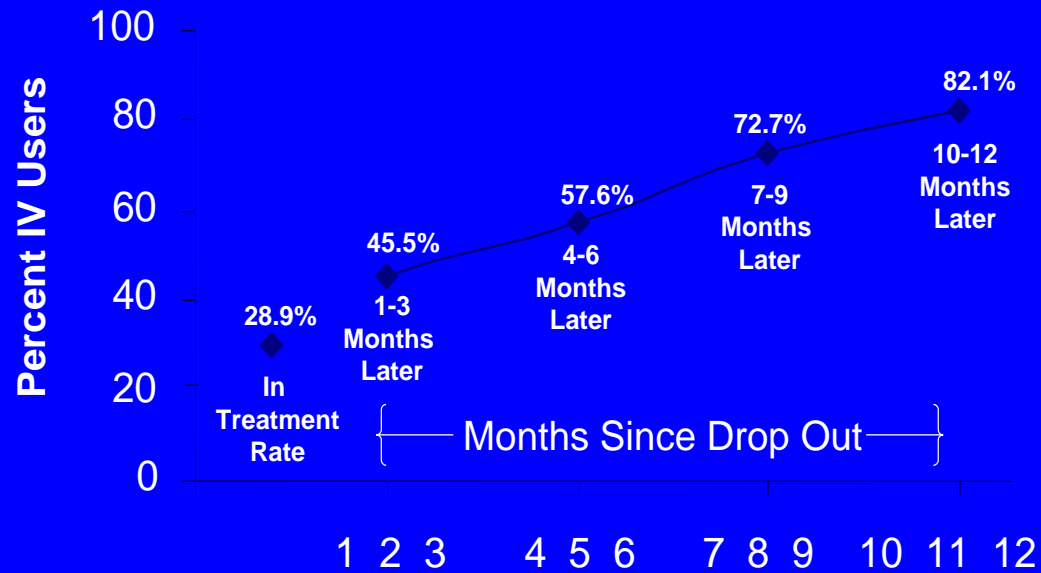
Efficacy of Methadone Concurrent Control Studies

- 100 male narcotic addicts randomized to methadone or placebo in a treatment setting
 - Both groups initially stabilized on 60 mg methadone per day
 - Both groups had dosing adjustments:
 - Methadone could go up or down
 - Placebo – 1 mg per day tapered withdrawal
- Outcome measures: treatment retention and imprisonment

<u>Weeks in Treatment</u>	<u>% Retention Methadone Group</u>	<u>Placebo Group</u>
32	76	10
156	56	2

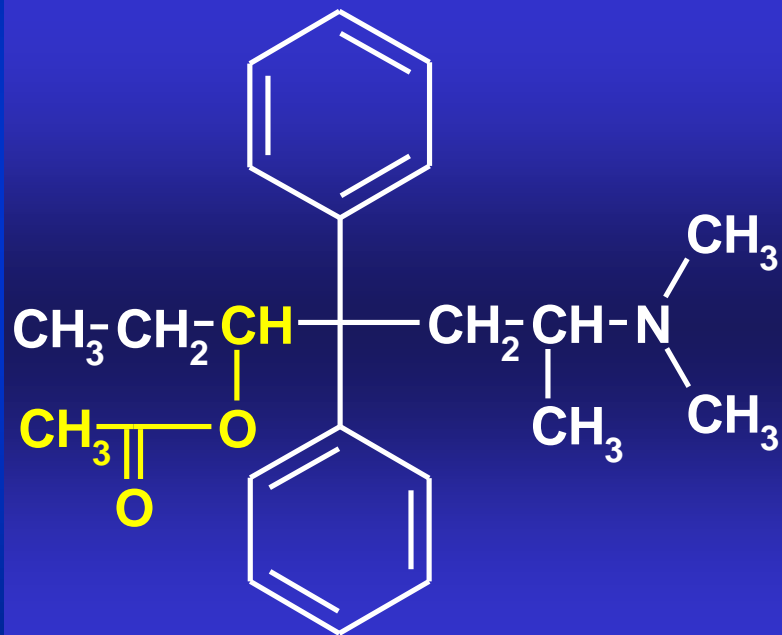
Imprisonment rate: twice as great for placebo group

Relapse to IV Drug Use After Termination of Methadone Maintenance Treatment

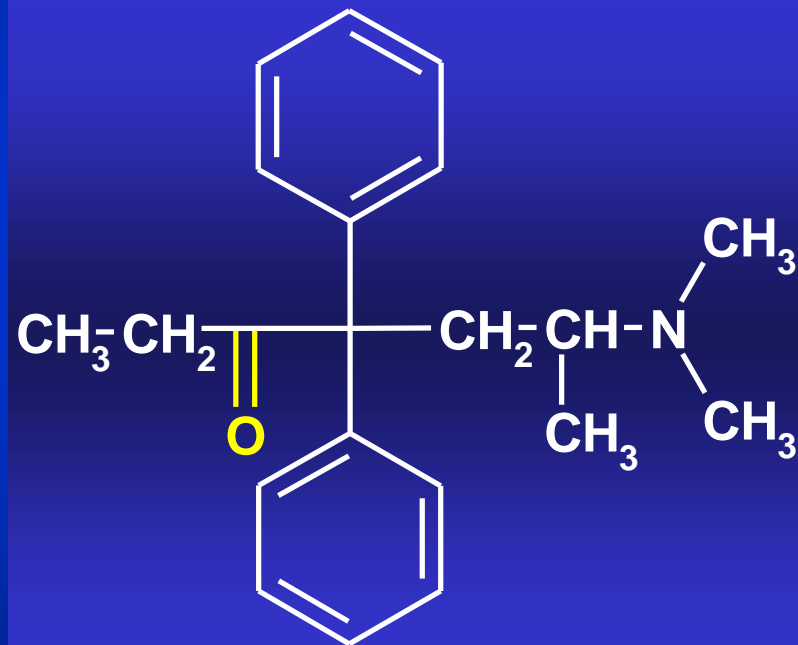


Ball, JC, Ross A. The Effectiveness of Methadone Maintenance Treatment, Springer-Verlag, New York, 1991

LAAM



METHADONE



LAAM Pharmacokinetics

- Converted to active metabolites
- Has 2-3 day duration of action
- Dosing usually three times per week but can be every other day to twice a week
- Recently received “Black Box” warning from US FDA for “torsade de pointes” arrhythmia (10 episodes out of 33, 000 patient exposures)

Narcotic Addiction, The Treatment Gap, and The Public Health Imperative

- 980,000 chronic opiate users in US in need of treatment
- At best, 180,000 in all forms of opiate treatment
- More than 800,000 users not in treatment
- 50% of all new HIV seroprevalence
(@ 20,000 infections)
- HCV prevalence in narcotic addict population
(90-95%)
- HBV parallels HIV infection in this population
- TB cases for opiate users (@ 30% PPD+)

Figure 3. Illicit Drug Use by Age, 1999

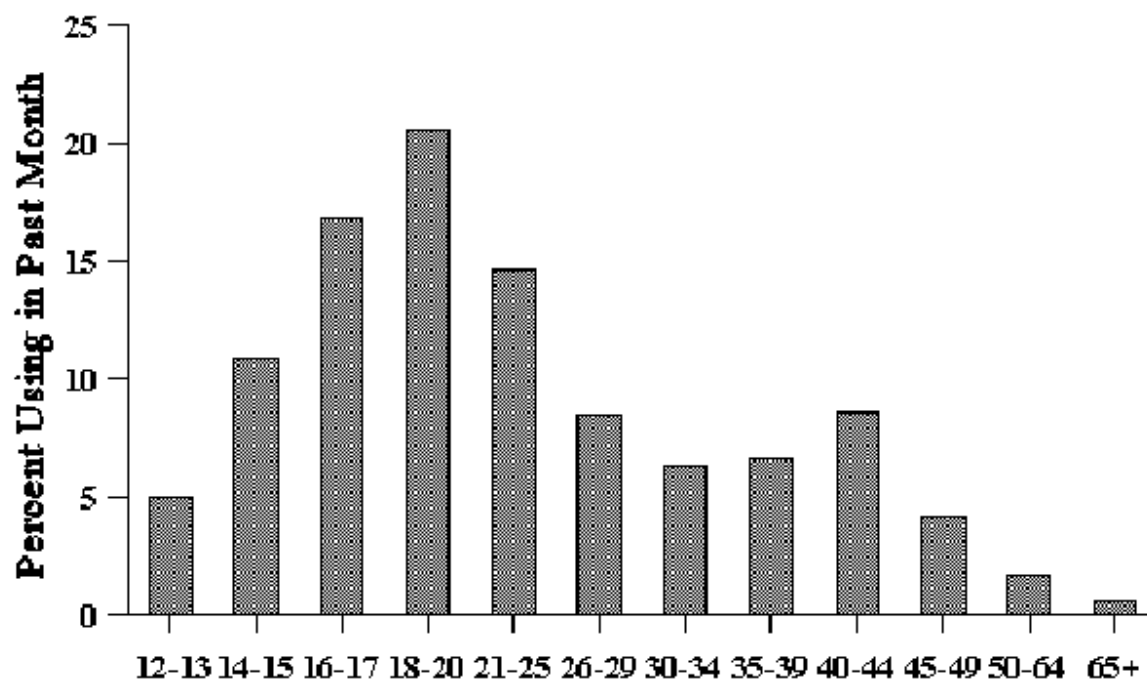
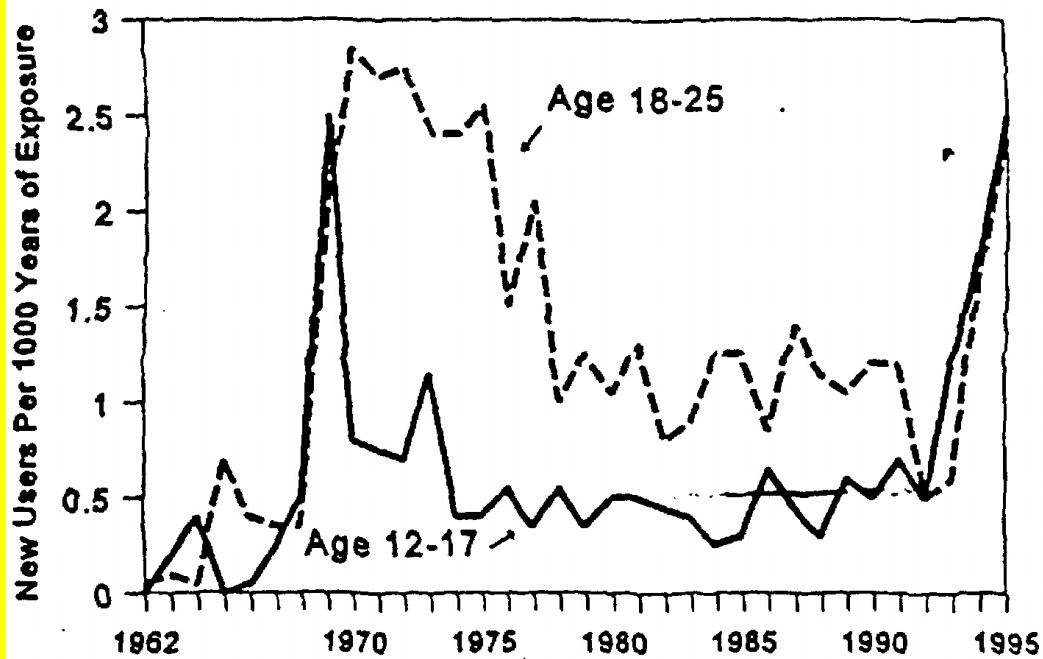
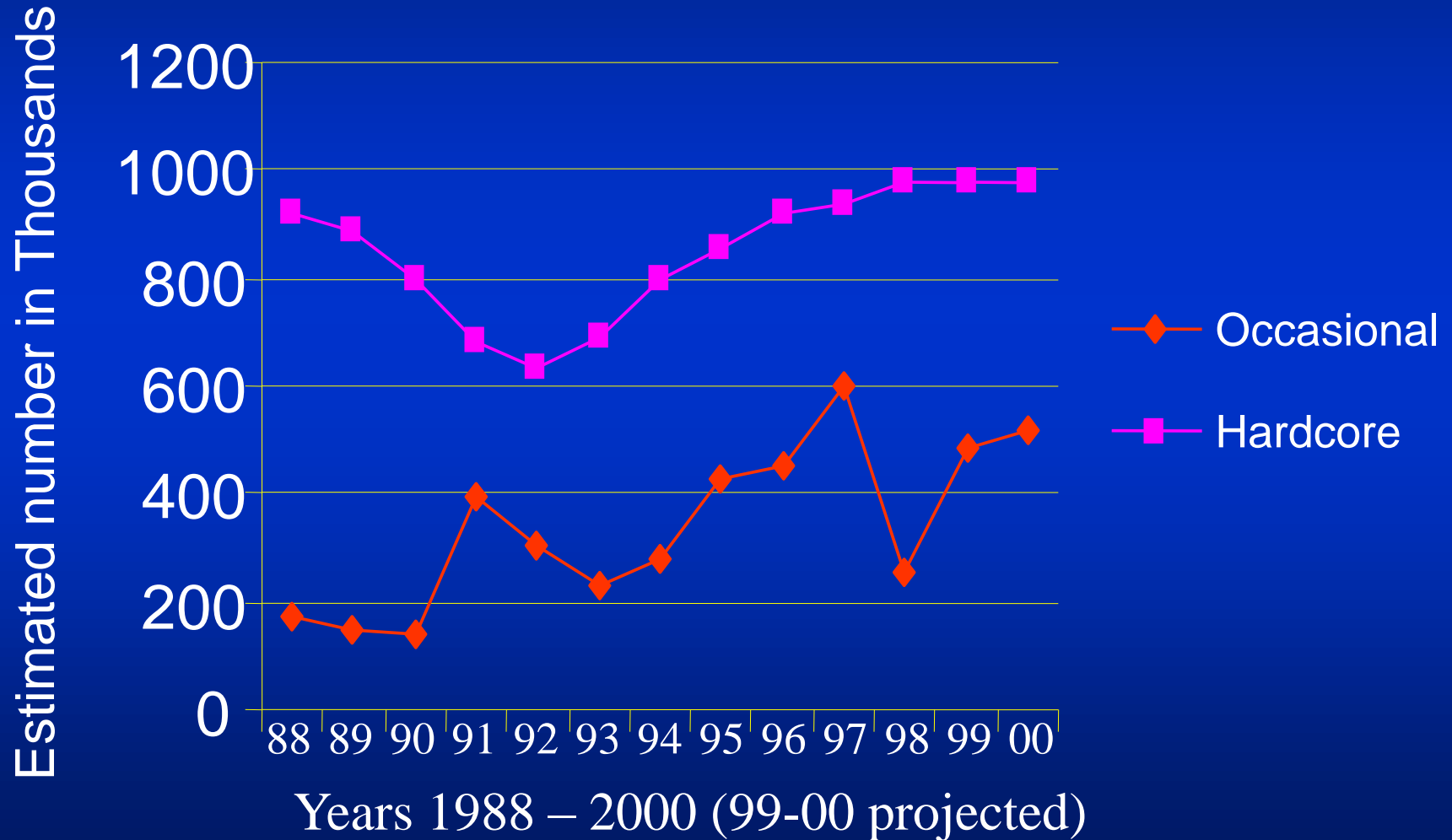


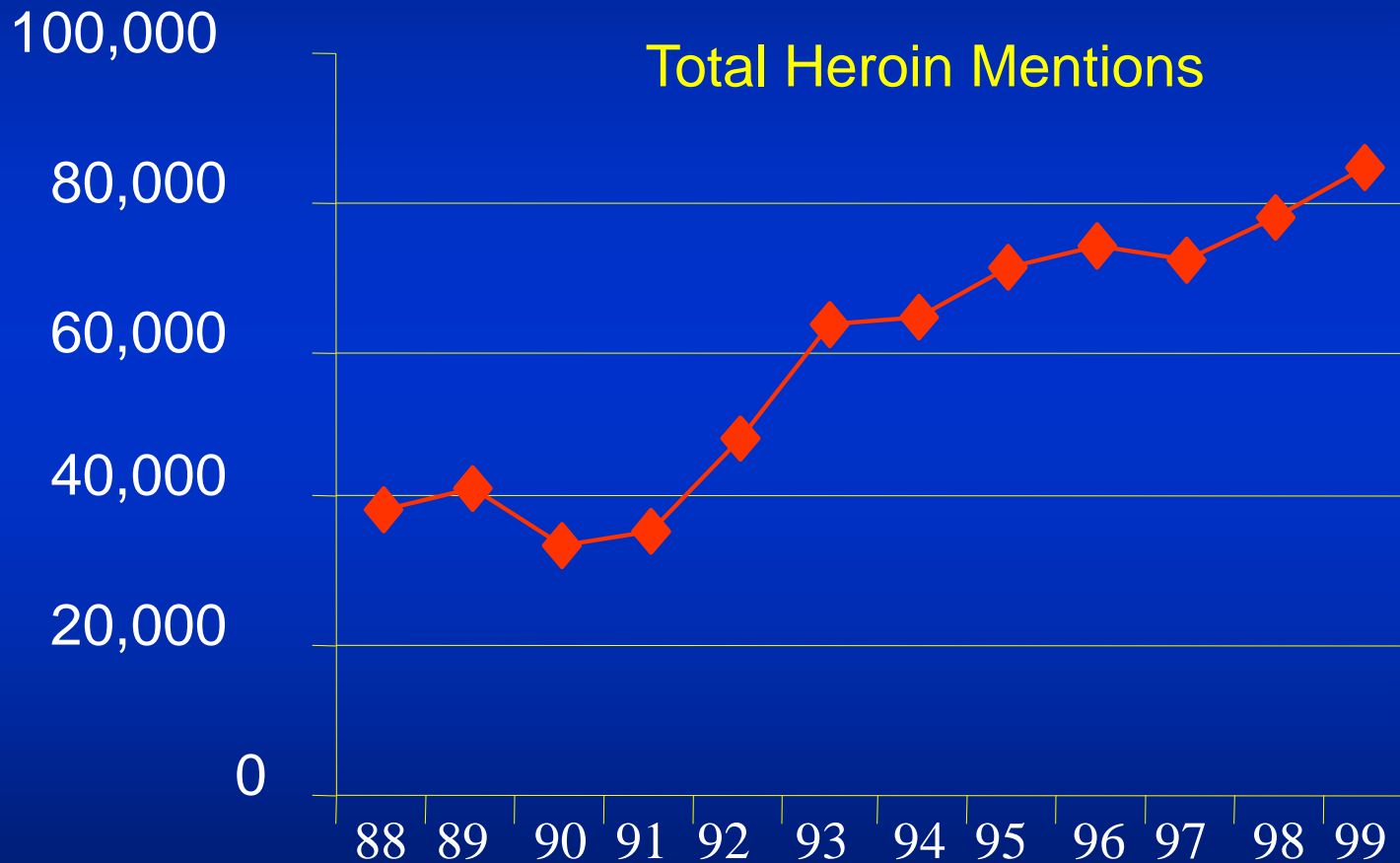
Figure 3. Age-specific Rates of First Heroin Use: 1962-1995



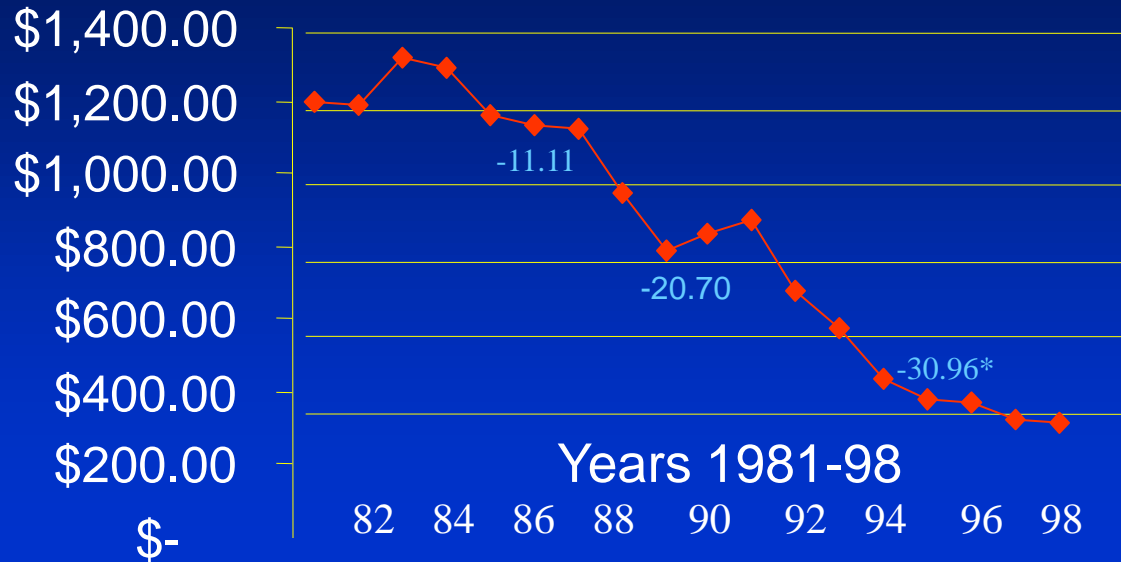
Treatment Need Rationale



Treatment Need Rationale



Price per Pure Gram/"Dealer" Level



Purity



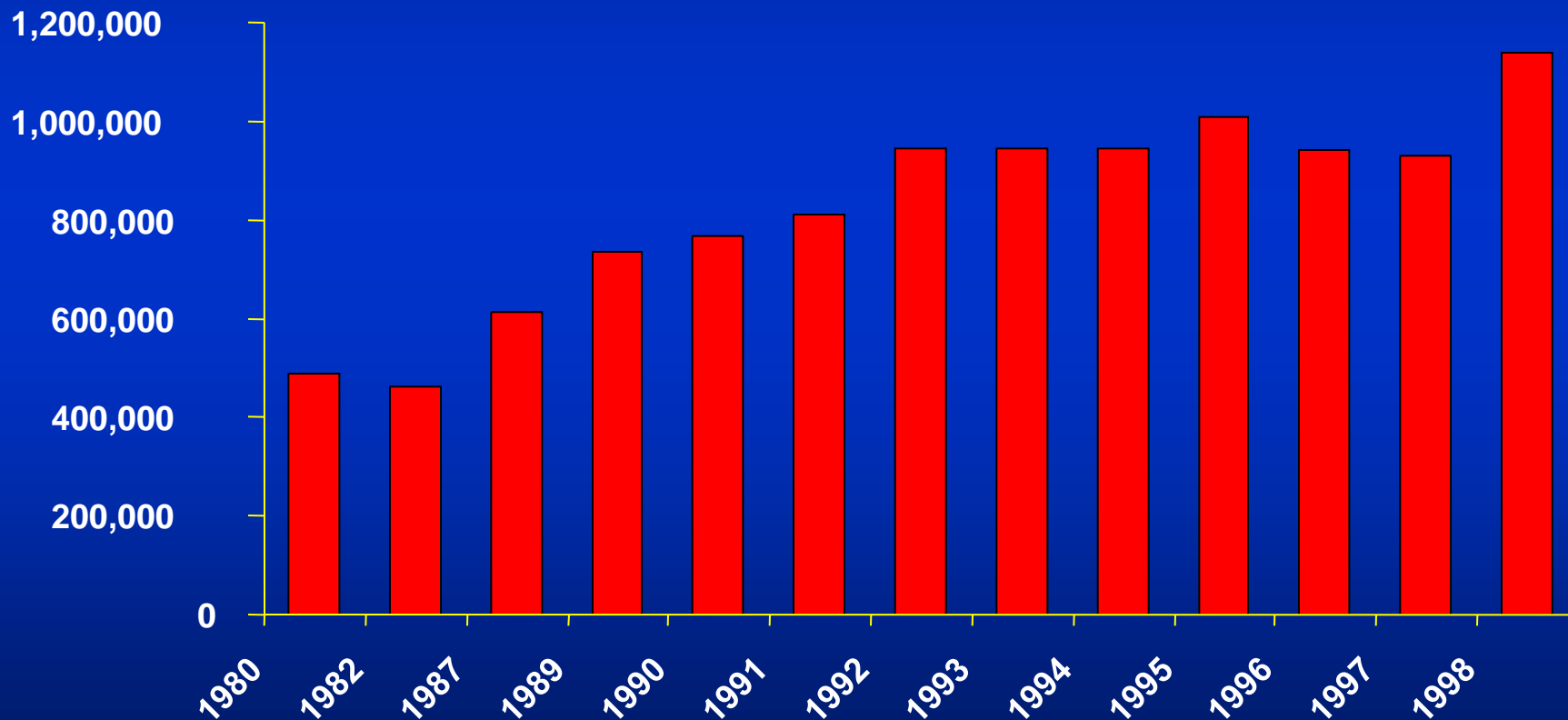
*significant change

Profile of Heroin Users in Treatment

Sex	66% = Male 34% = Female
Race	45.3% = White 26.6% = Hispanic 25% = Black
Age	22.3% = 35-39 years 19.8% = 30-34 years 19.6 = 40-44 years
Frequency of Use	83.9% = Daily
Employment	53.7% = Not in labor force
Education	42.7% = High school/GED
Marital Status	53.7% = Never married
Source of Income	33.4% = Public assistance
# of Prior Treatment Episodes	29% = 5 or more

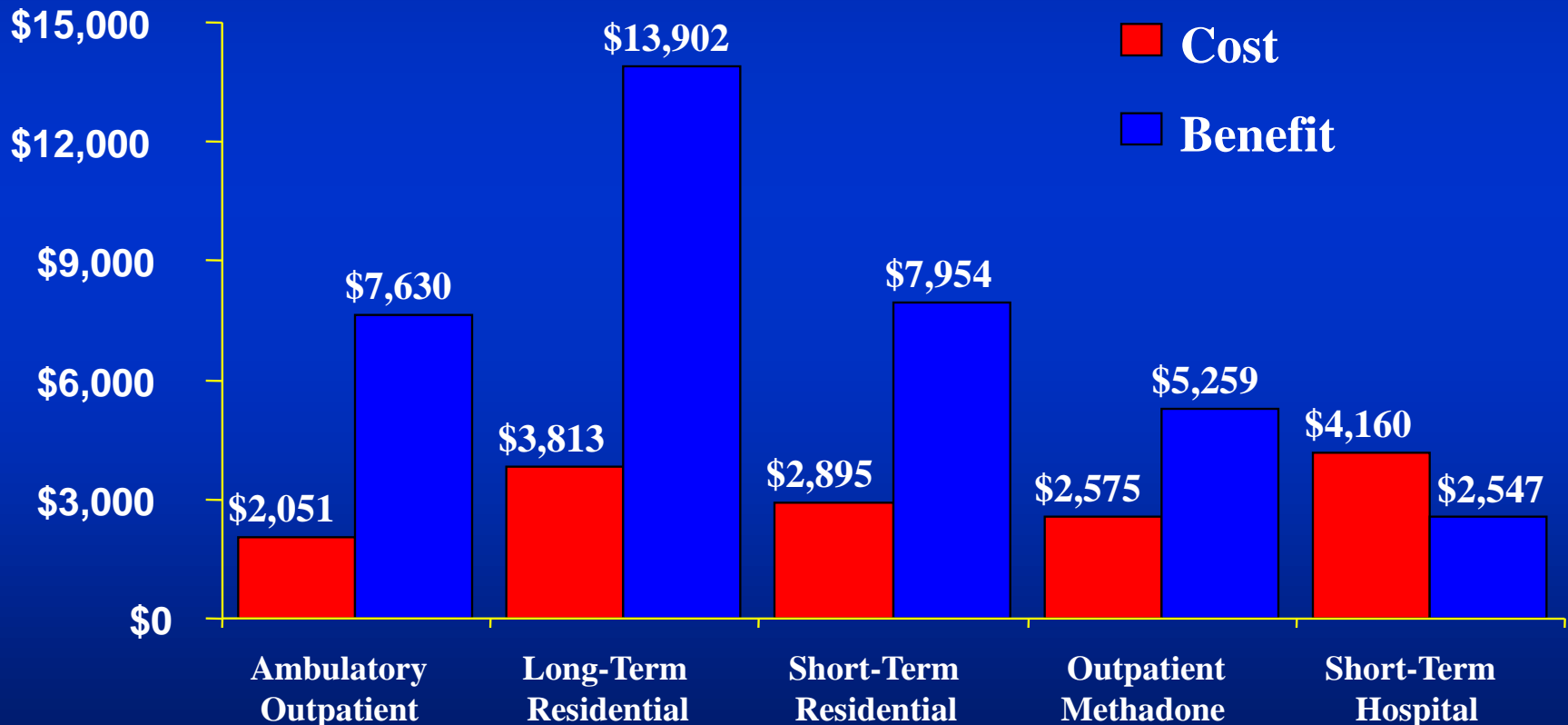
More than 1 Million Persons are in Treatment, Every Day

Clients in Specialty Treatment for Drugs and Alcohol
(one-day census of active clients)



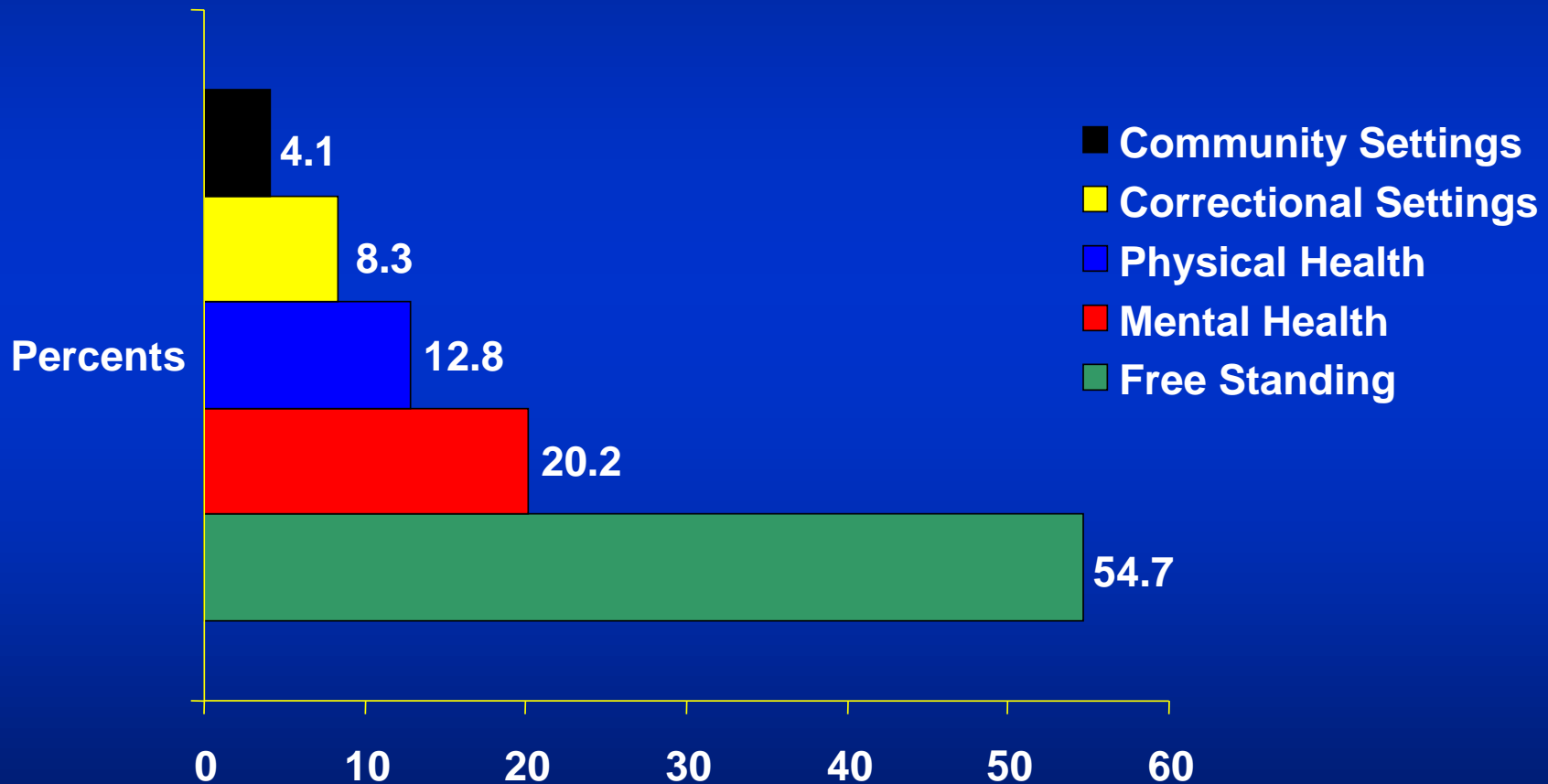
DHHS/SAMHSA, 1995-98

On Average, the Benefits of Drug Treatment Outweigh the Costs by a Margin of 3 to 1.

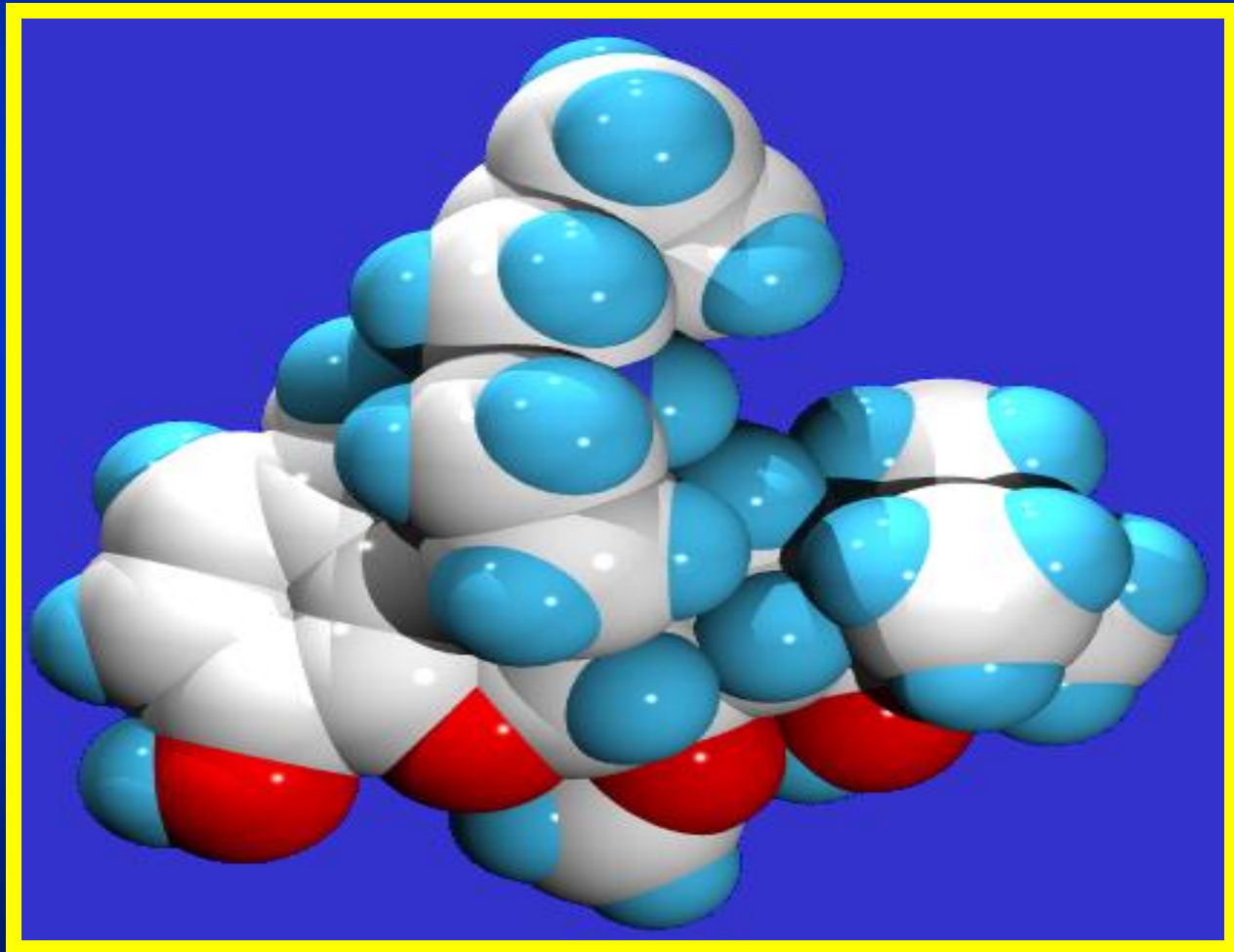


More than Half Those in Treatment are Being Treated in Outpatient Settings

Percentage of Clients in Treatment, by Facility Setting



Buprenorphine



Buprenorphine – Current Status

- Schedule V narcotic drug under the US CSA
- Approved as an analgesic in US and 40 other countries
- Approved for opiate dependence treatment in 26 countries (buprenorphine mono tablets)
- NDA for buprenorphine mono (2 and 8 mg tablets) - “approvable”
- NDA for buprenorphine/naloxone - (bup/nal: 2 mg/0.5 mg and 8 mg/2 mg) “approvable”

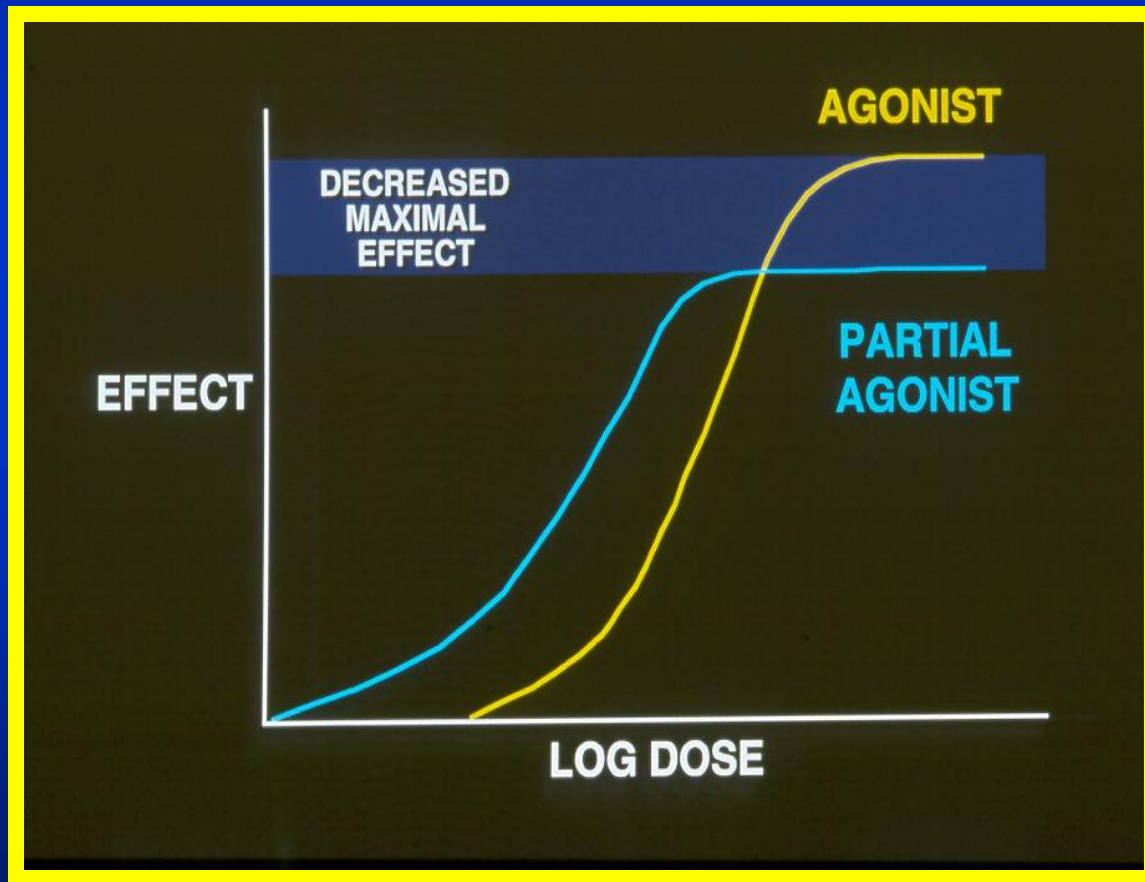
Buprenorphine – Therapeutic Niche

- Unmet need for a medication between methadone/LAAM (full agonists) and naltrexone (competitive antagonist)
- Partial agonist would fit the unmet need

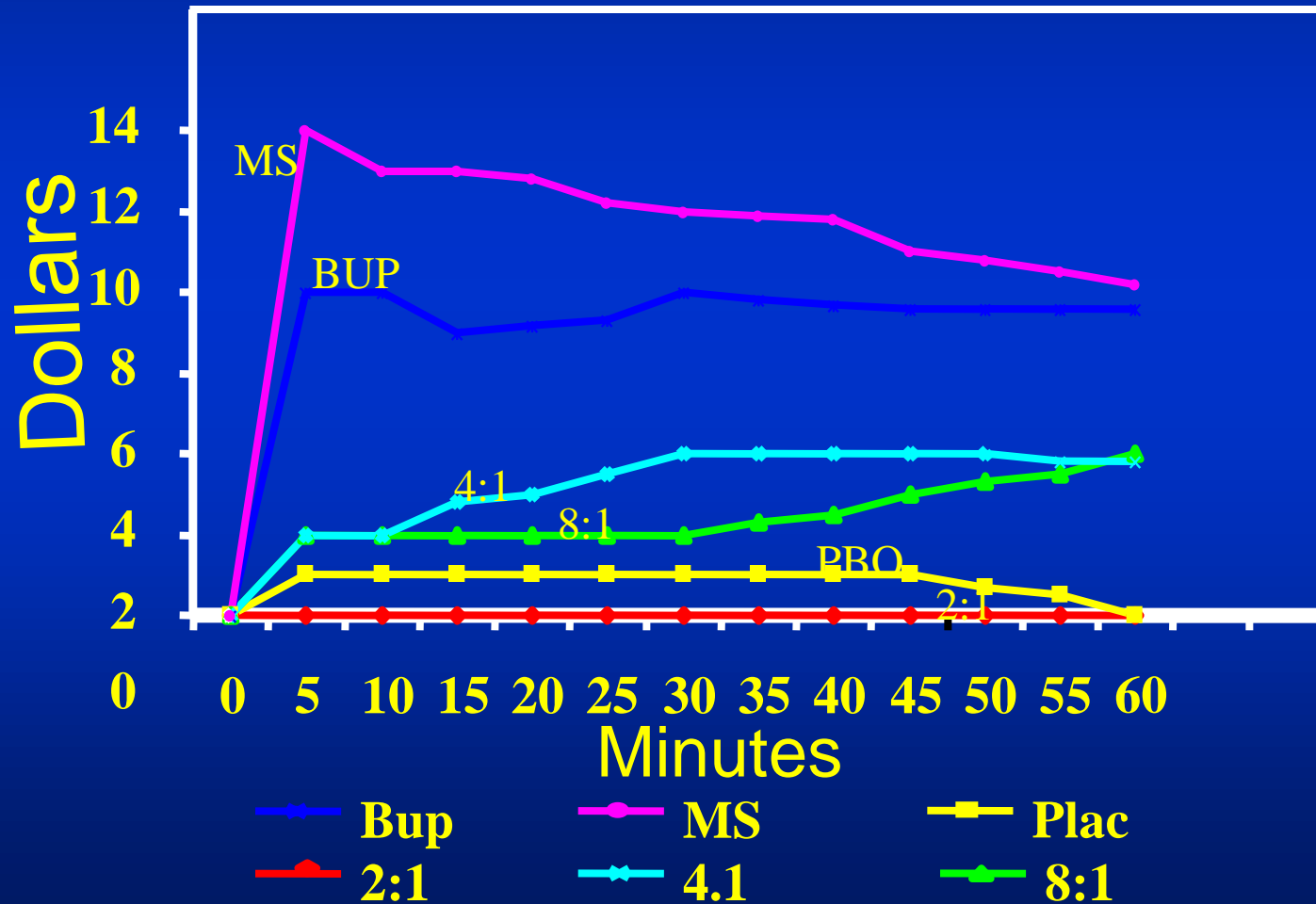
Why Buprenorphine Was Developed

Animals studies showed:

- Partial agonist properties
- Slow “off-rate” from *Mu* receptor
- Limited or non-existent physical dependence
- Less toxic than other opiates



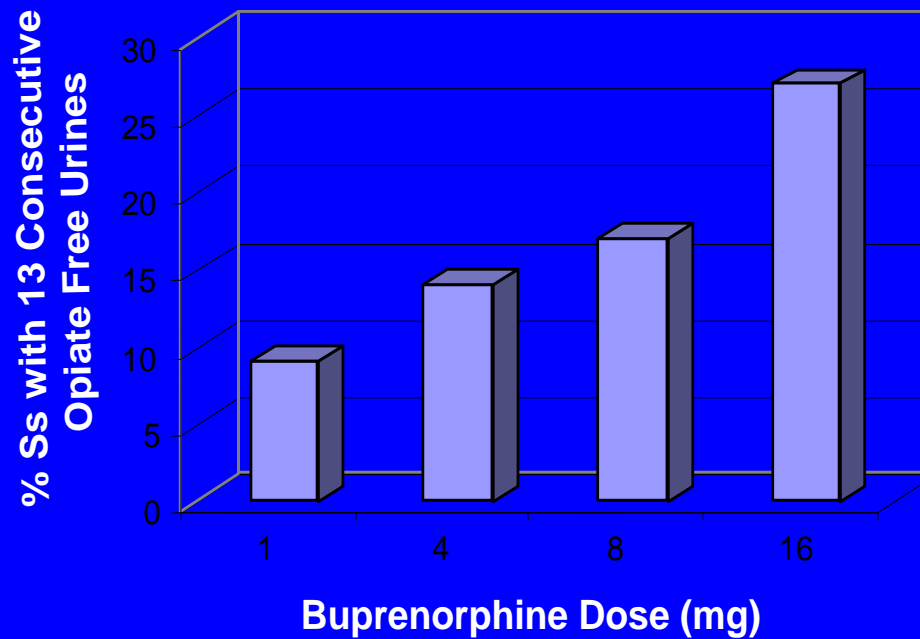
Value of a Dose in Dollars



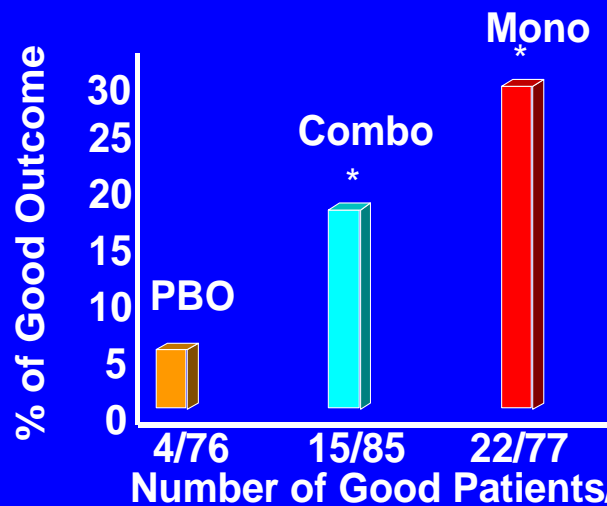
Addition of Naloxone Reduces Abuse Potential

- Naloxone will block buprenorphine's effects by the IV but not the sublingual route
- Sublingual absorption of buprenorphine @ 70%; naloxone @ 10%
- *If injected*, BUP/NX will precipitate withdrawal in a moderately to severely dependent addict

Study #999A: Buprenorphine's Effect on Opiate Use



Study #1008 Buprenorphine (≥ 8 Urines)



PBO = 5.26 Combo = 17.65 Mono = 28.57

<u>Statistics</u>	<u>Value</u>	<u>Prob</u>
Chi-Square	13.641	0.001
Mantel-Haenszel	13.591	0.001

Current Needs

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Non-opiate medications for opiate dependence

Medications to Treat Withdrawal

Medications to Treat Relapse

Bup NX Best Practices Study #1018

To mimic actual practice after Bup NX is approved

- Phase 4 Design
- Non-traditional Settings
- Open Label w/ Rx Dispensing of Bup (up to 24mg/day)
- Flexibility (detox vs. maintenance)
- Adolescents included from age 15

583 patients.

6 states (Washington, California, New York, Florida, Illinois, Texas).

38 Physicians' offices.

33 community / clinic pharmacies.

Bup NX Best Practices Study #1018, **Interim Results**

- 16-week retention rate is currently 70% (goal for the same period, as stated in protocol, was 51%)
- Drug use appears to have decreased significantly
 - 31.4% reported *not using opiates* at the 30 day follow-up after completion of treatment
 - 41% reported *not using other non-opiate drugs* at the 30 day follow-up after completion of treatment
- HIV risk behavior appears to have decreased significantly

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Medications to Treat Withdrawal

Medications to Treat Relapse

Political Environment

Children's Health Act of 2000

Expands research and health care for children...

- Substance abuse – youth drug treatment programs
- Mental health

Special Populations...

Children

Pregnant women

Patients with co-morbid disorders

Objectives:

- To assess buprenorphine for safety in the mother and fetus
- To assess the neonatal abstinence syndrome following exposure to buprenorphine

Controlled Trial Design:

- Parallel Group
 - 1) Methadone
 - 2) Buprenorphine
 - 3) Non-pharmacotherapy treatment
- Vouchers targeted at all drugs
- Dose
 - Methadone 40 - 100 mg daily
 - Buprenorphine 4 - 24 mg daily

Study Criteria:

Inclusion:

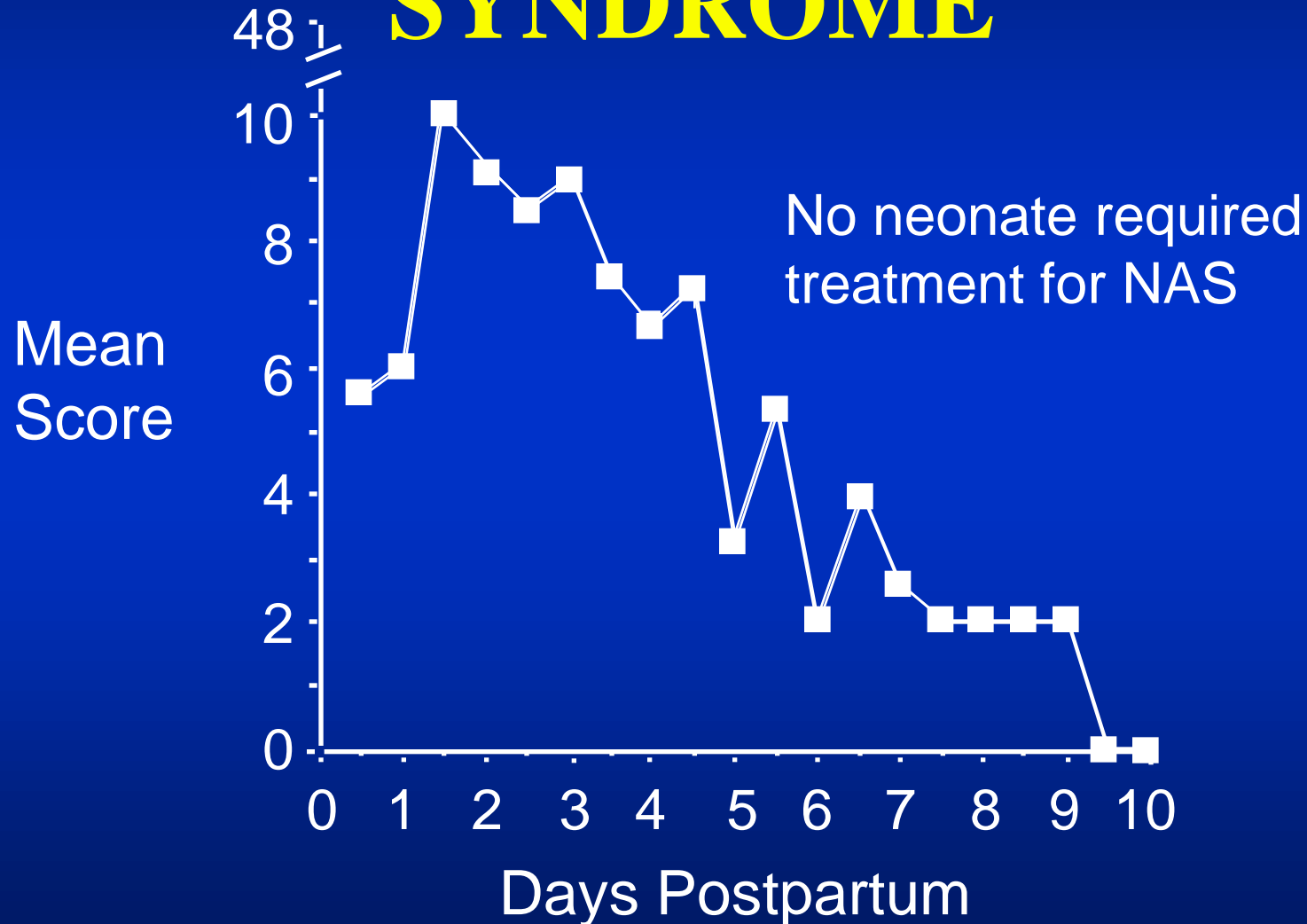
- 18 - 40 years of age
- Gestational age 16 - 30 weeks
- Opioid dependent (DSM-IV, SCID I)
- Recent opioid use
- Opioid positive urine

Study Criteria:

Exclusion:

- Undocumented methadone positive urine at admission
- Serious medical or psychiatric illness
- Diagnosis of preterm labor
- Evidence of congenital fetal malformation
- Diagnosis of alcohol abuse or dependence
- Limited benzodiazepine use

TIME COURSE OF NEONATAL ABSTINENCE SYNDROME



Conclusions:

- Mild, short-lived NAS that may differ from methadone
- Sufficiently safe to conduct a double-blind randomized controlled trial

Special Populations – Co-Morbid Disorders...

High rates of depression are seen in both treatment seeking and non-treatment seeking opiate dependent subjects

Potential Treatment: Nefazodone

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Medications to Treat Relapse

Lofexidine

- Alpha 2 agonist similar to clonidine
- Less hypotensive effects
- Current Phase III trial of 3.2 mg lofexidine versus placebo in an opiate dependent population undergoing withdrawal
- May be tested for prevention of relapse

Lofexidine

Phase III

- 11 Day Inpatient study
- 96 Opiate-Dependent subjects, 64 enrolled
- Sites: UCLA, UPenn, Columbia

Study initiation: May 2001

Completion Date: October 2002

Current Needs

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Medications for special populations

Medications to Treat Withdrawal

Non-opiate medications for opiate dependence

Medications to Treat Relapse

Non-Opiate Medications...

Exempt from provisions of the NATA

Less abuse liability?

Available to a greater number of dependent individuals?

Potential Non-opiate Medications:

Alpha-2-Adrenergic Agonists - Lofexidine

NMDA Antagonists - Memantine

Ultra Rapid Opiate Detoxification
(UROD)

Current Needs

Greater availability of treatment

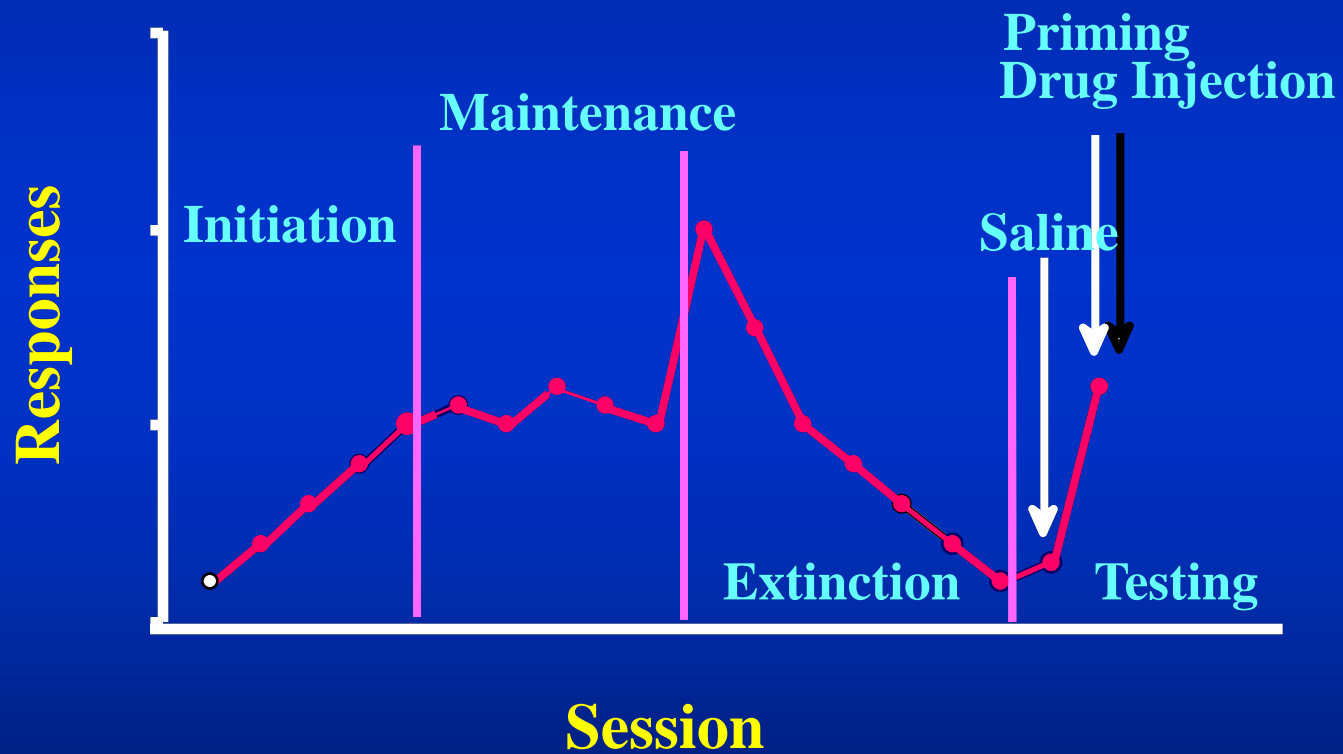
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Non-opiate medications for opiate dependence

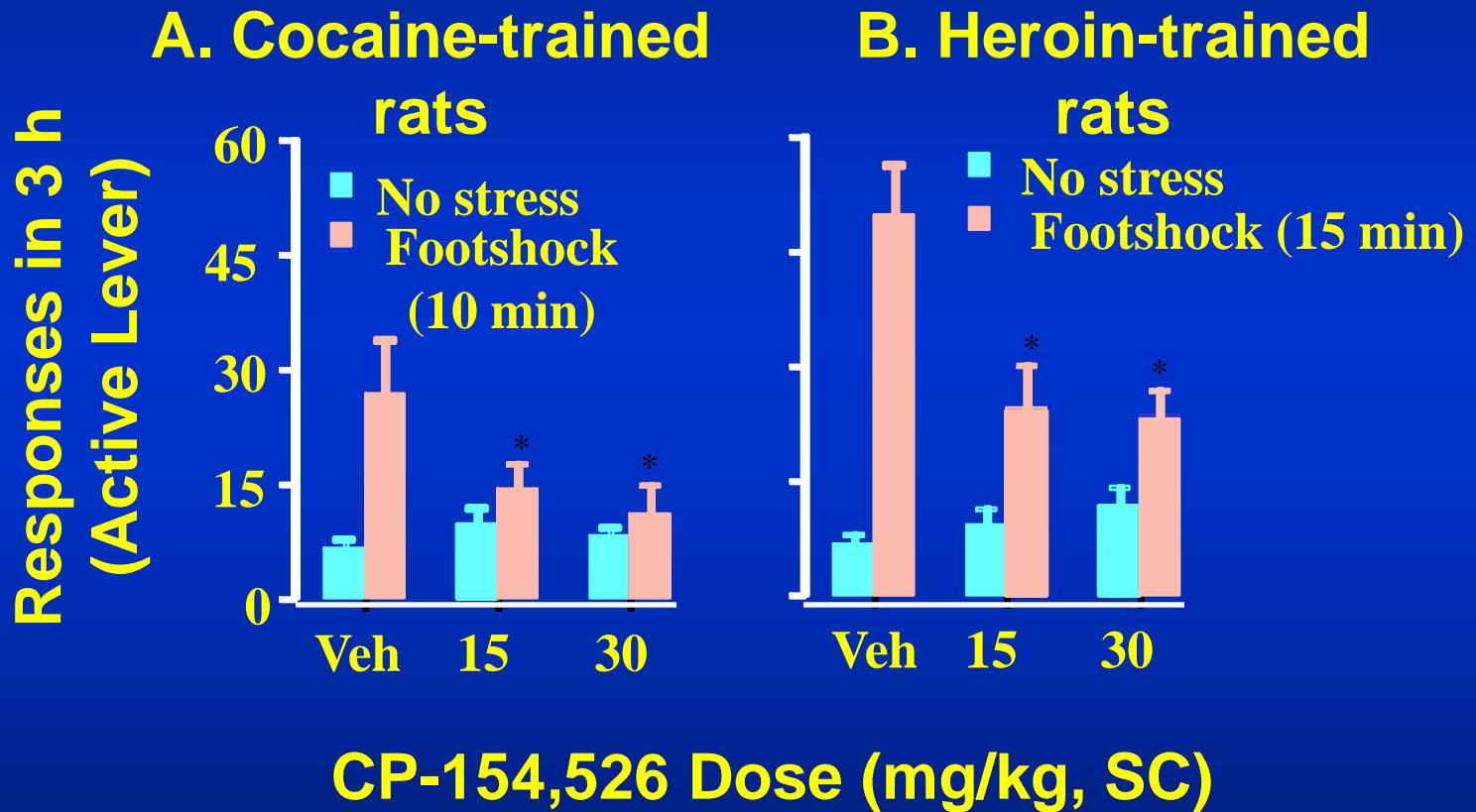
Medications to Treat Withdrawal

Medications to Treat Relapse

Hypothetical Time Course in the Reinstatement Procedure



Effects of SC Injections of the Non-Peptide CRF Antagonist, CP-154,526, on Stress-Induced Reinstatement



Relapse Medications...

Important for use after detoxification from opiates has been achieved

High recidivism rate – 82% relapse to iv opiates within 1 year after discontinuing methadone

Only 1 approved medication to date

Relapse Medications...

Opiates:

Naltrexone (FDA approved)

Non-Opiates:

Alpha-2-adrenergics - Lofexidine

NMDA Antagonists - Memantine

CRF Antagonists

Depot Naltrexone

- Oral naltrexone has been available for over 15 years
- Depot dosage forms are desirable due to treatment adherence issues
- Naltrexone has been shown to reduce relapse in a criminal justice population

Depot Naltrexone

Resulting from SBIR & contract programs

Biotek

Alkermes

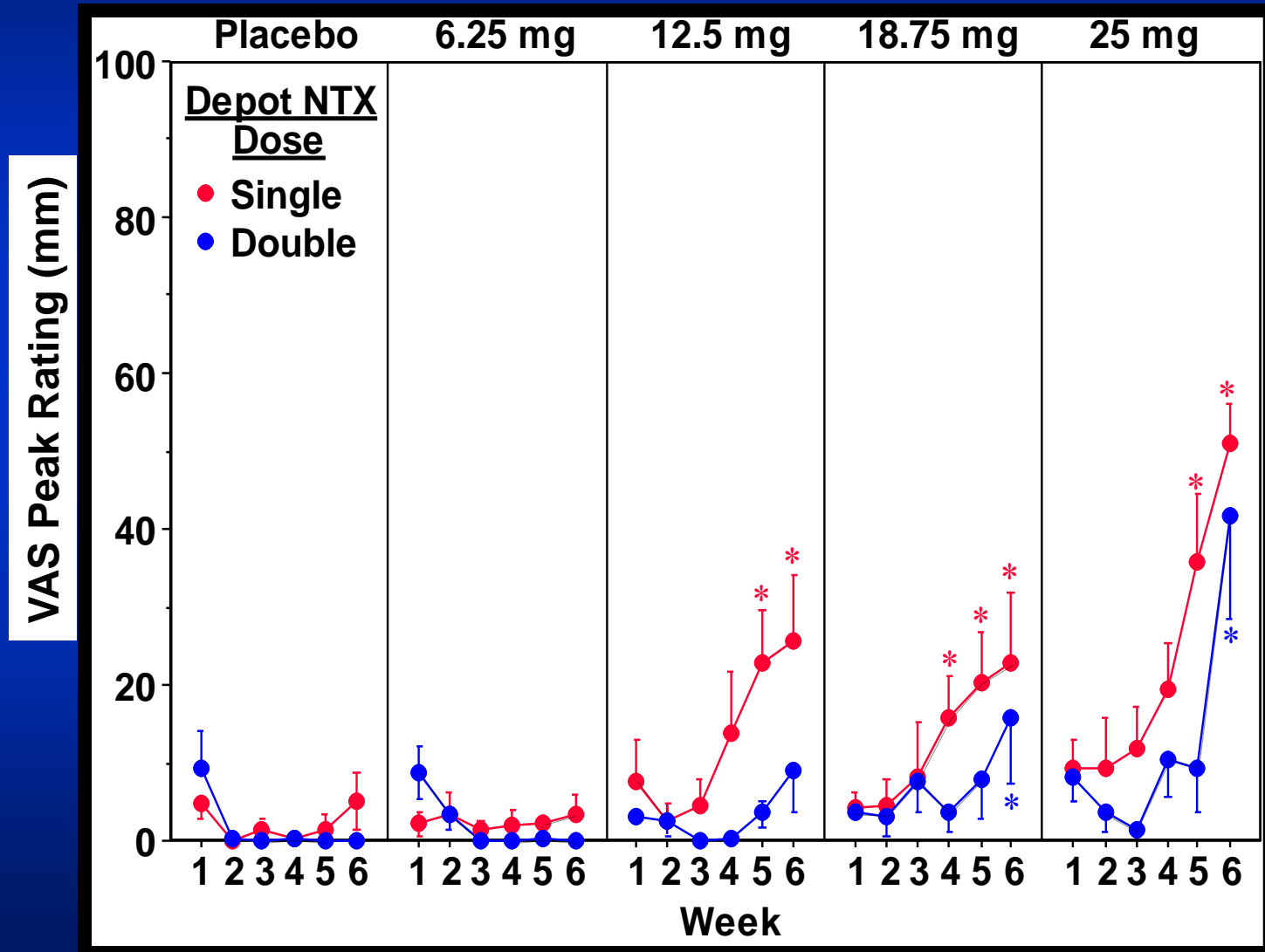
Drug Abuse Sciences

Data from Phase 1 & 2A indicated that:

- No side-effects other than the discomfort associated with the injection
- Dose-response: Compared to the single dose, the double dose of depot naltrexone produced a more effective and longer-lasting antagonism to the effects of opiate

Data from NY study on heroin challenge shown in next slide

Double Dose (384 mg) Antagonized IV Heroin "high" for up to 5 weeks



Depot Naltrexone

Phase 2 outpatient trial (**Biotek**)

Two months outpatient trial

60 subjects, 18 enrolled

Sites: UPenn (O'Brien) and Columbia (Kleber).

Completion date: December 2002

Phase 2A

Alkermes: To be initiated at IRP/Hopkins

Drug Abuse Sciences (Phase 2A completed)

Proposed Future Directions...

Bup and Bup NX

Facilitate introduction into Office-based settings

Encourage Federal / State Interactions

Search for non-opiate medications to:

Treat opiate withdrawal

Reduce probability of relapse

Evaluate Treatment Potential of CRF Antagonists

Stress-induced Drug Seeking

Evaluate Treatment Potential of Kappa Antagonists