Opioid Dependence and Its Treatment

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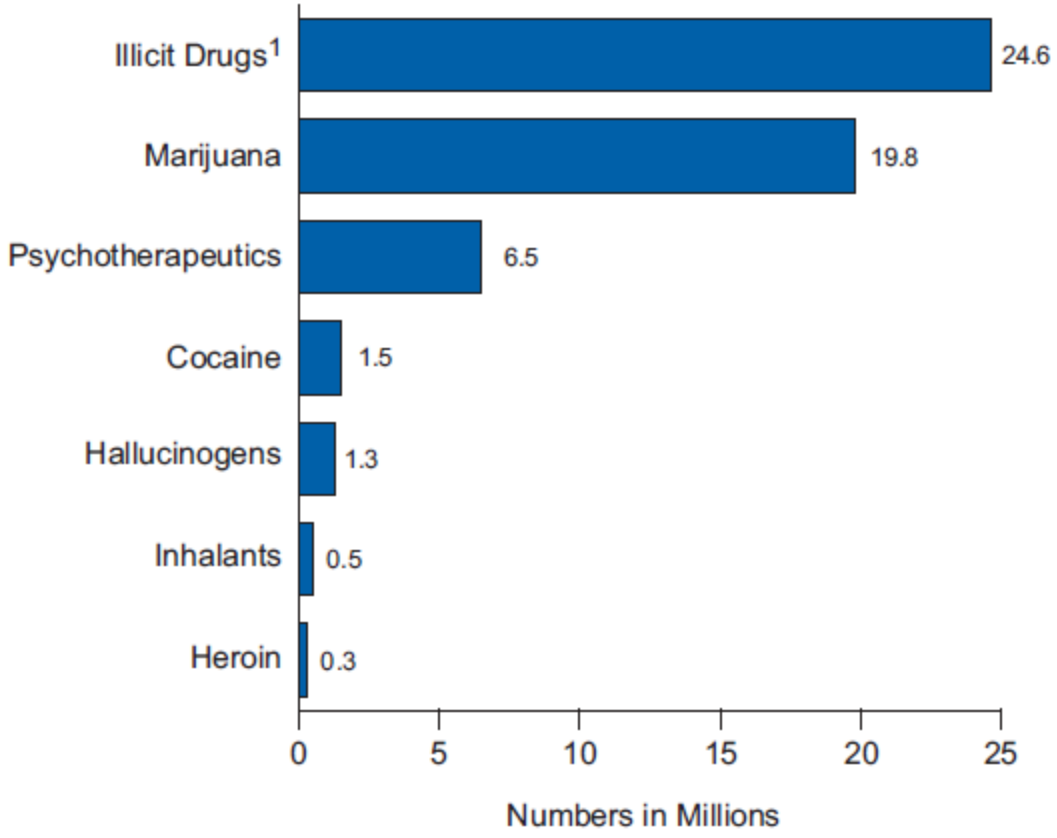
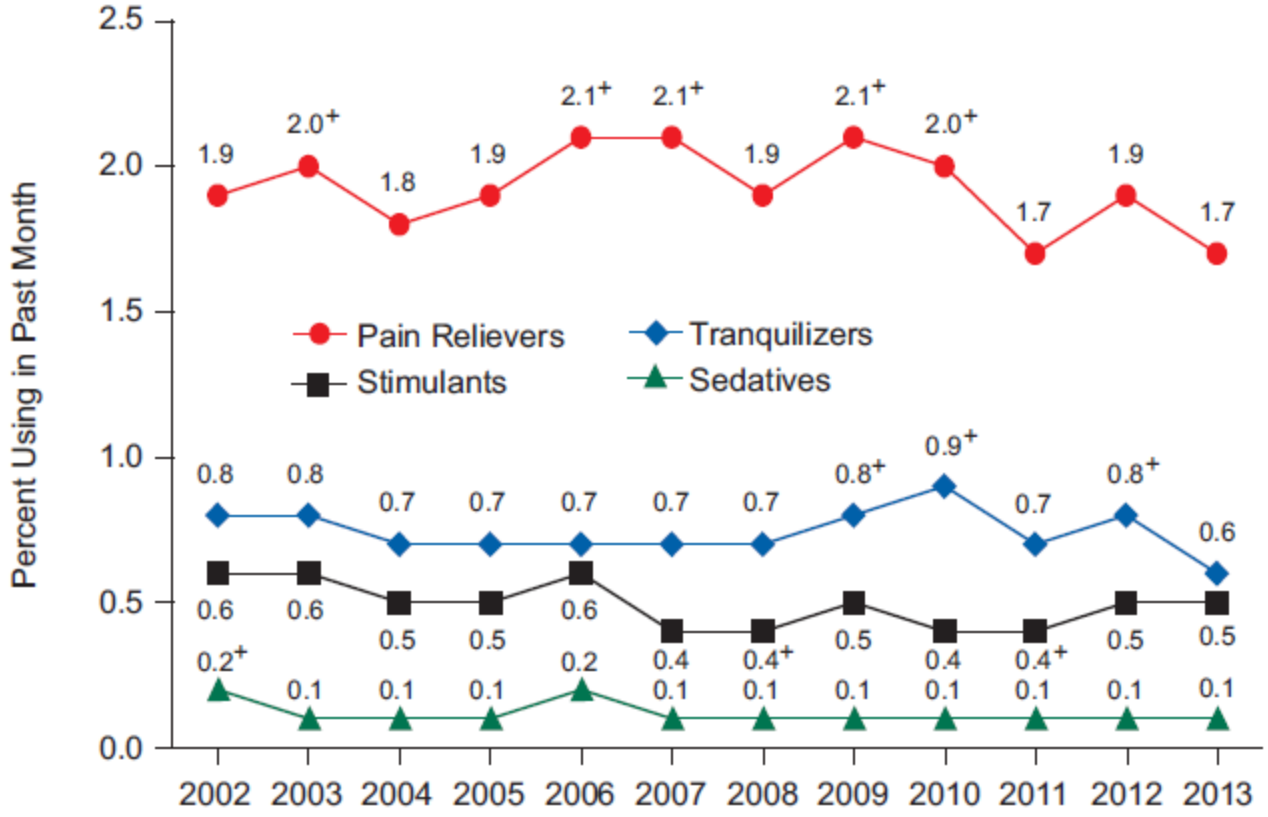
Figure 2.1 Past Month Illicit Drug Use among Persons Aged 12 or Older: 2013



[1] Illicit Drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.

NSDUH 2013

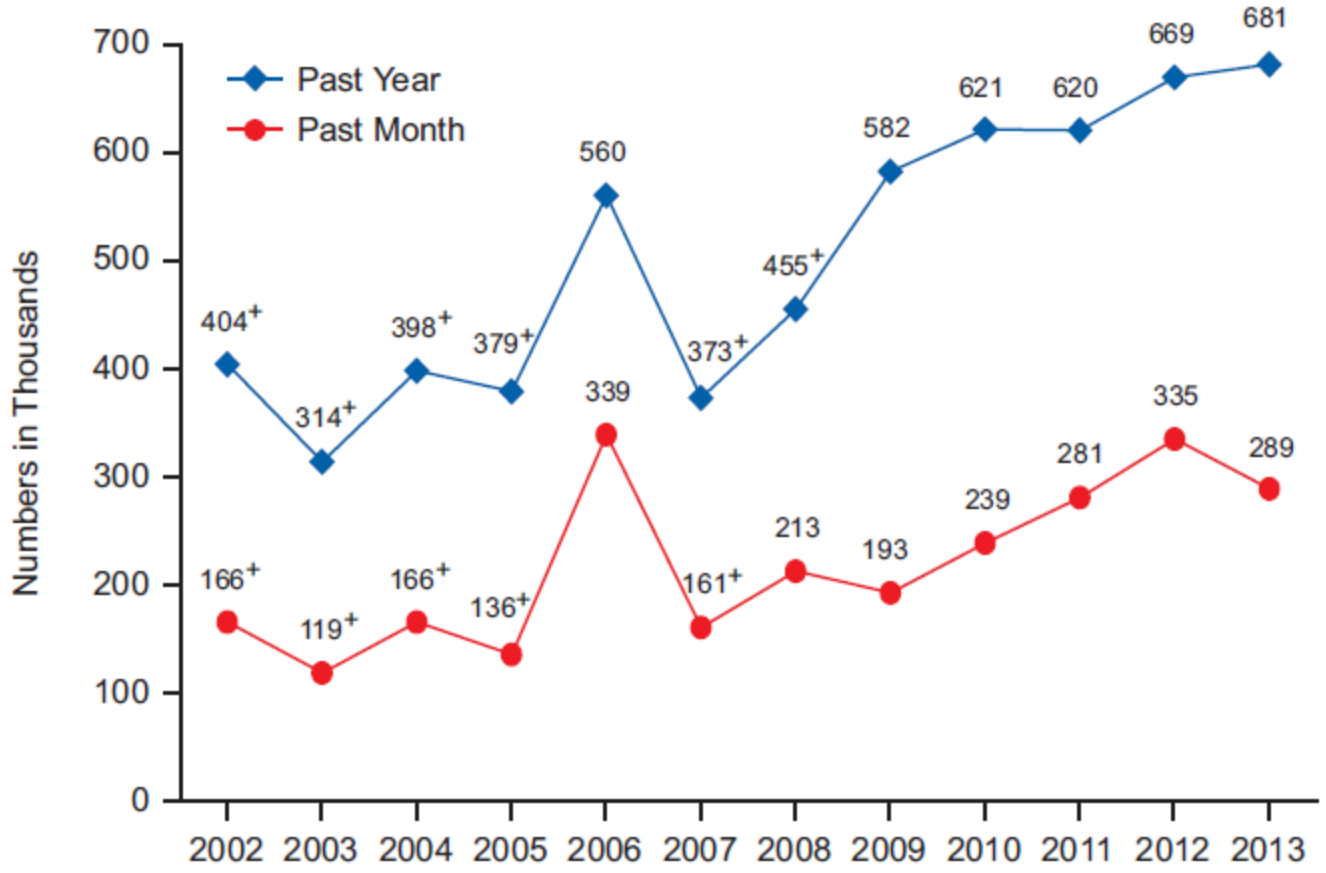
Figure 2.3 Past Month Nonmedical Use of Types of Psychotherapeutic Drugs among Persons Aged 12 or Older: 2002-2013



+ Difference between this estimate and the 2013 estimate is statistically significant at the .05 level.

NSDUH 2013

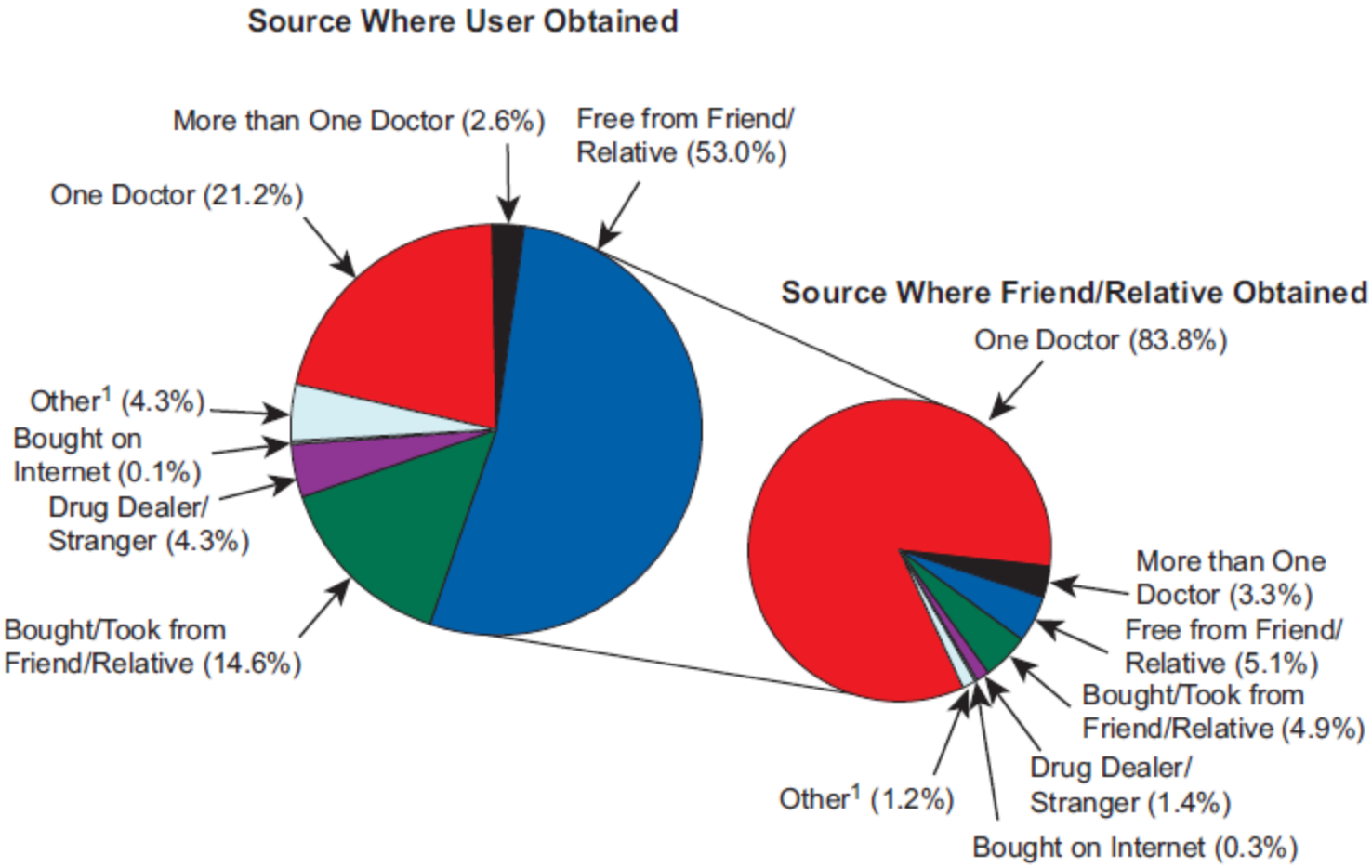
Figure 2.4 Past Month and Past Year Heroin Use among Persons Aged 12 or Older: 2002-2013



+ Difference between this estimate and the 2013 estimate is statistically significant at the .05 level.

NSDUH 2013

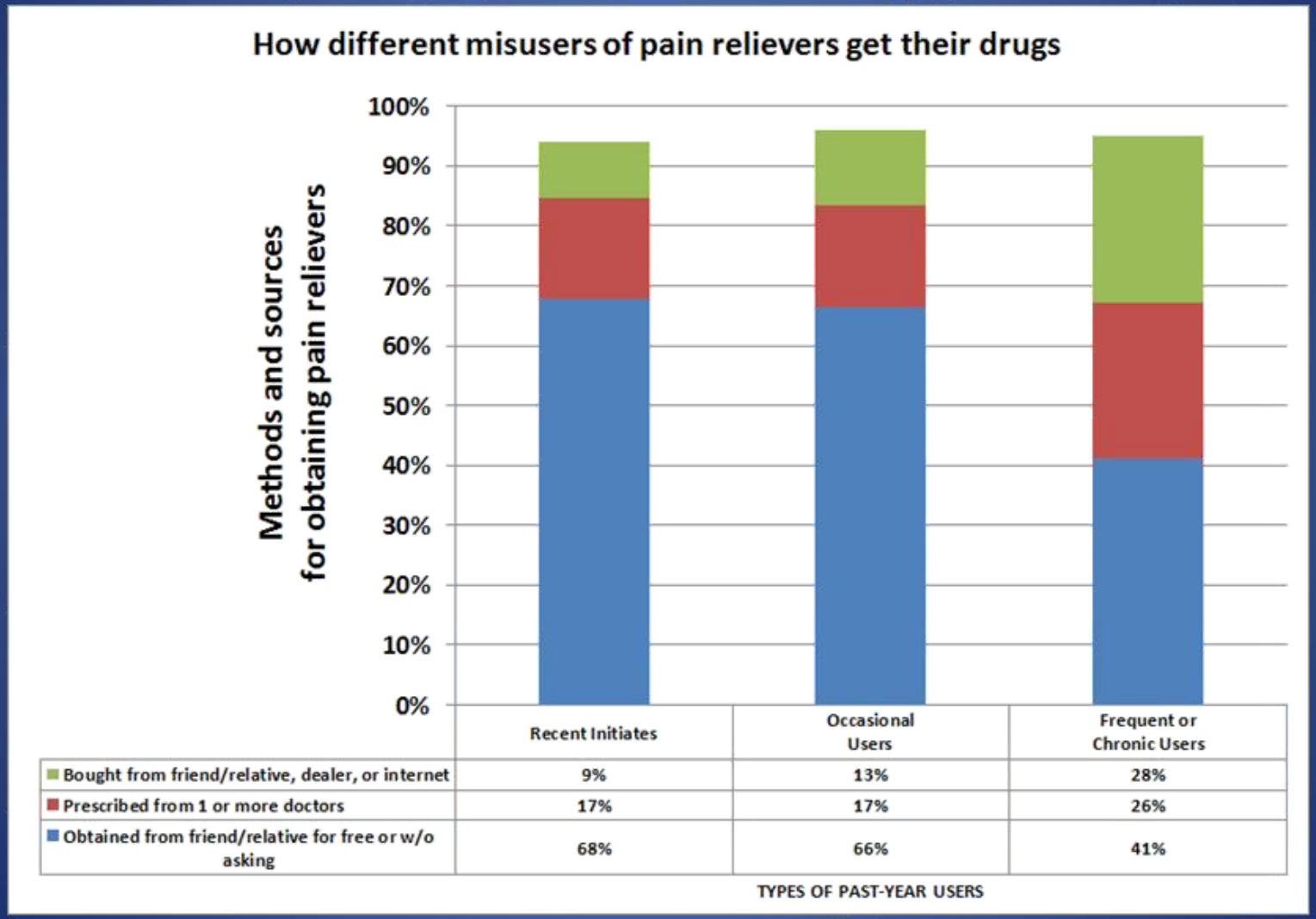
Figure 2.16 Source Where Pain Relievers Were Obtained for Most Recent Nonmedical Use among Past Year Users Aged 12 or Older: 2012-2013



[1] The Other category includes the sources "Wrote Fake Prescription," "Stole from Doctor's Office/Clinic/Hospital/Pharmacy," and "Some Other Way."

Note: The percentages do not add to 100 percent due to rounding.

Source of Prescription Pain Relievers



Source: SAMHSA, Center for Behavioral Health Statistics and Quality, *National Survey on Drug Use and Health, 2009-2010.* Unpublished special tabulations (March 2012).

Commonly Abused Opioids

Diacetylmorphine (Heroin)

Hydromorphone (Dilaudid)

Oxycodone (OxyContin, Percodan, Percocet, Tylox)

Meperidine (Demerol)

Hydrocodone (Lortab, Vicodin) – recently moved from C-III to C-II

Commonly Abused Opioids (continued)

Morphine (MS Contin, Oramorph)

Fentanyl (Sublimaze)

Propoxyphene (Darvon)

Methadone (Dolophine)

Codeine

Opium

Commonly Abused Opioids

Opioids are abused by all routes of administration including oral, inhalation, smoking, and injection.

Heroin is most commonly used intranasally or intravenously, but can be inhaled, smoked, or injected intramuscularly or subcutaneously.

Opium is usually smoked.

The pharmaceutical opioids are usually taken orally (but may also be injected).

Psychiatric Assessment – Features of Disorders

Opioid intoxication and withdrawal

It is important to recognize and distinguish symptoms of opioid intoxication and withdrawal, since their symptomatic presentations can overlap with the signs and symptoms of other psychiatric disorders.

Psychiatric Assessment – Features of Disorders

Opioid intoxication

Signs and symptoms:

- Feeling of “high” or euphoria
- Pupillary constriction
- Drowsiness or coma
- Slurred speech
- Impaired attention or memory

Psychiatric Assessment – Features of Disorders

Opioid withdrawal

Occurs after stopping or decreasing use that has been occurring regularly (e.g., daily for weeks) – this is spontaneous withdrawal

Note it can also occur if person receives a dose of an opioid antagonist or partial agonist – this is precipitated withdrawal

Psychiatric Assessment – Features of Disorders

Opioid withdrawal

Signs and symptoms:

- Dysphoric mood
- Nausea or vomiting
- Muscle aches/cramps
- Lacrimation
- Rhinorrhea

Psychiatric Assessment – Features of Disorders

Opioid withdrawal (continued)

- Pupillary dilation
- Sweating, piloerection
- Diarrhea
- Yawning
- Fever
- Insomnia

Endogenous Opioid System

- Unknown early 70's, remained unproven
  - Recognized, opiate receptor binding sites in the brain discovered
- Three distinct families of opioid peptides
  - Enkephalins
  - Endorphins
  - Dynorphins

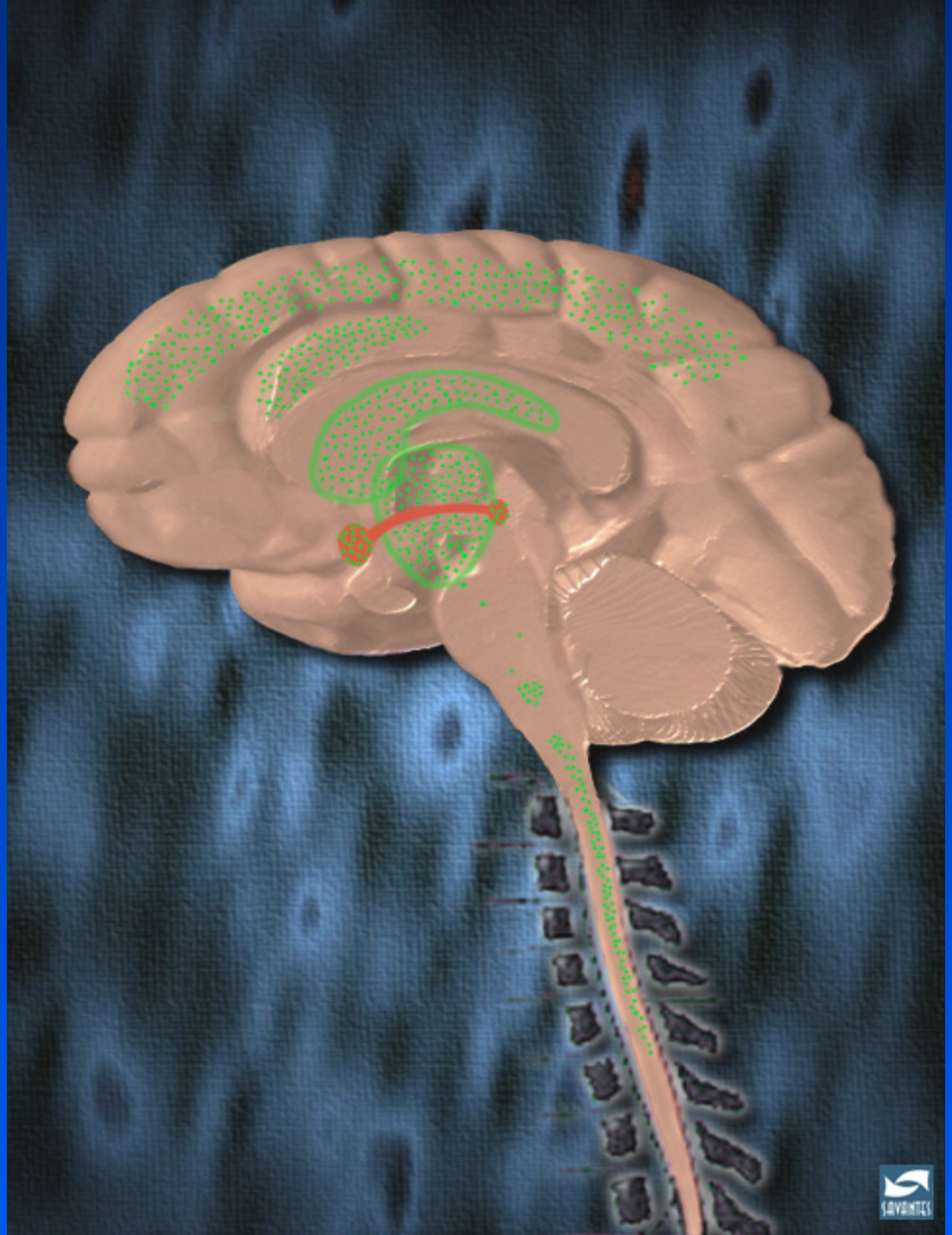
Reference: Opioid Analgesics, Chapter 21, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th edition.

Opioid Receptors

- **Mu – (MOR) Subtypes: μ_1, μ_2**
- **Kappa – (KOR) Subtypes: κ_1, κ_2, κ_3**
- **Delta – (DOR) Subtypes: δ_1, δ_2**

Reference: Opioid Analgesics, Chapter 21, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th edition.

http://www.opioids.com/receptors/index.html



Opioid Effects upon Physiological Systems

- Produce analgesia
- Affect mood
- Affect rewarding behavior
- Alter respiratory function
- Alter cardiac function
- Alter gastrointesintal function
- Alter neuroendocrine function

References: Opioid Analgesics, Chapter 21, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th edition.

Tafton JA, Abhinav R, Methadone: A New Old Drug With Promises and Pitfalls, Current Pain and Headache Reports 2009 13:24-30

Respiratory

- Direct effect on brainstem respiratory centers
  - Reduction in responsiveness to carbon dioxide
- Depress all phases of respiratory activity (rate, minute volume, tidal exchange)
- Rate may fall to 3 - 4 breaths/min
- Underlying pulmonary dysfunction

Opioid Physiological Effects

- **Cough**
  - Depress cough center in the medulla
- **Anti-Nausea/Emetic**
  - Stimulation of chemoreceptor trigger zone in the medulla
- **Skin**
  - Dilatation of cutaneous blood vessels
    - Sweating, pruritus
- **Cardiovascular**
  - ↑Peripheral vasodilation
  - ↓Peripheral resistance
- **Gastrointestinal**
  - ↓Decrease gastric motility, prolongs gastric emptying
  - Bilary tract, constricts Sphincter of Odi, epigastric distress to typical biliary colic

References: Opioid Analgesics, Chapter 21, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th edition.

Tafton JA, Abhinav R, Methadone: A New Old Drug With Promises and Pitfalls, Current Pain and Headache Reports 2009 13:24-30

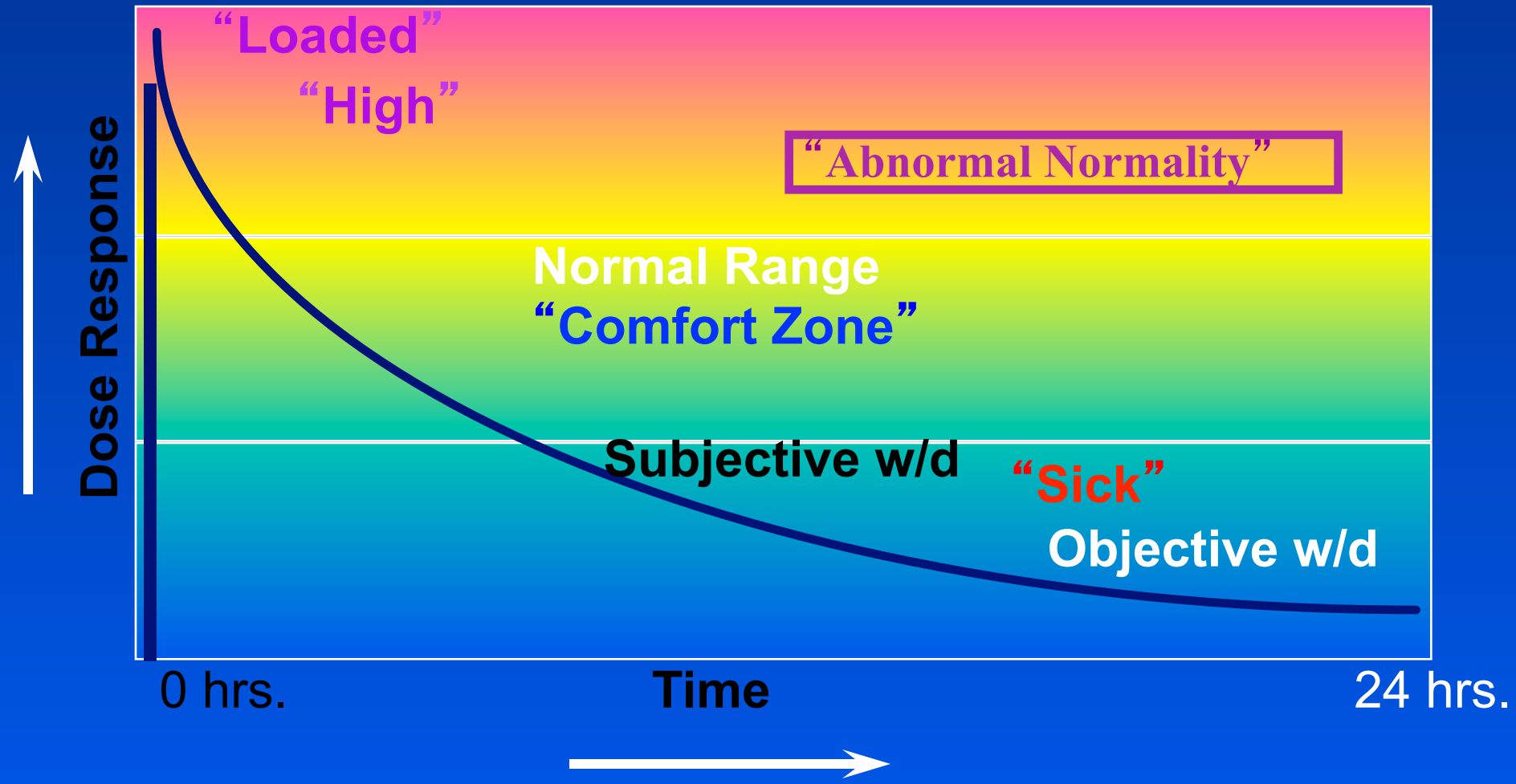
Opioid Physiological Effects

- **Ureter / Urinary Bladder**
  - ↑Smooth muscle tone, combined with antidiuretic → decrease urine flow
- **Immune System**
  - Complex, acute and chronic
  - Overall suppression
  - Different opioid agonist have unique immunomodulatory properties
- **Hypothalamus**
  - Morphine inhibits GnRH, CRH → ↓LH, FSH, ACTH and β-endorphins
    - Pituitary concentrations of testosterone and cortisol decline
  - **Women (Methadone)**
    - Chronic administration, tolerance develops, menstrual cycles normalize after disruption due to heroin
  - **Men (Methadone)**
    - Chronic administration, tolerance to hypothalamic releasing factors develops, circulation concentrations of LH and testosterone are wnl
  - **Antidiuretic effect** → urinary retention

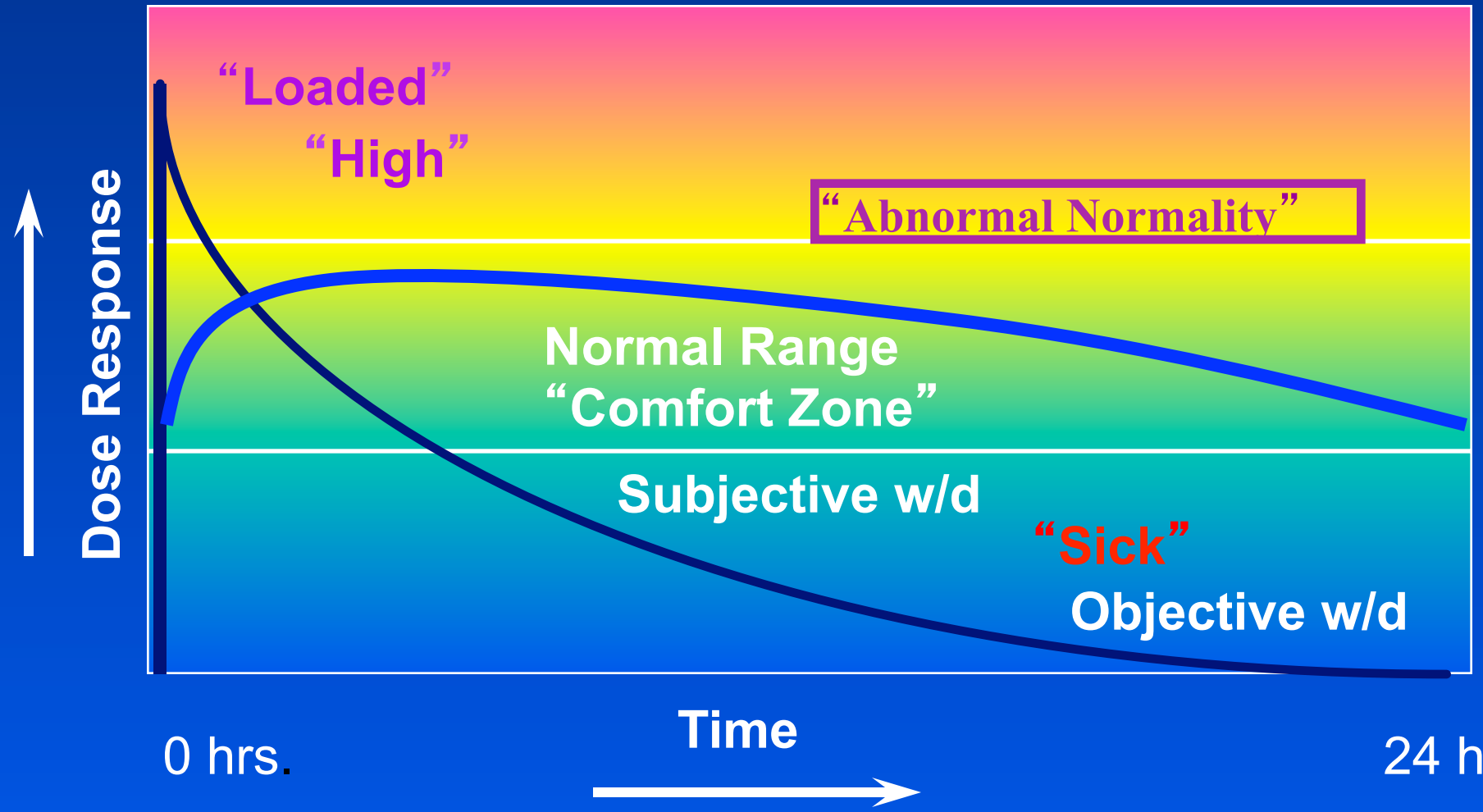
References: Opioid Analgesics, Chapter 21, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th edition.

Tafton JA, Abhinav R, Methadone: A New Old Drug With Promises and Pitfalls, Current Pain and Headache Reports 2009 13:24-30

Heroin Simulated 24 Hr. Dose/Response
With established heroin tolerance/dependence



Methadone Simulated 24 Hr. Dose/Response
At steady-state in tolerant patient



Medication Options

- Agonists:
  - Methadone
  - Buprenorphine
- Antagonists:
  - Naltrexone, p.o.
  - Naltrexone depot

Rationale for opioid agonist medications

Advantages of opioid agonist medication over heroin

- Non-parenteral administration
- Known composition
- Gradual onset and offset
- Long-acting
- Mildly reinforcing
- Medically supervised

Rationale for opioid agonist medications

Opioid agonist treatment

- Most effective treatment for opioid dependence
- Controlled studies have shown significant:
  - Decreases in illicit opioid use
  - Decreases in other drug use
  - Decreases in criminal activity
  - Decreases in needle sharing
  - Improvements in prosocial activities
  - Improvements in mental health

Methadone

OUTCOMES

Effectiveness of Treatment:

Early Efficacy & Outcome Studies

- Retention - VS. TC and Drug Free
  - NYC, DARP, & TOPS (>40K patients)
- Retention relative to dose/placebo
  - Newman, Strain, & Caplehorn
- Reincarceration and heroin use
  - Dole, Newman & Whitehill (‘69 & ‘76)

Efficacy: Retention Studies

Methadone Modality

Study	Size	Treatment	Dropout %/wk
NYC	20,603	MMT	0.76
Newman	100	MMT	0.85
		Placebo	7.1

Efficacy: Retention Studies
Methadone Modality by Dose

Study	Size	Treatment	Dropout %/wk
Strain	212	50 mg/d	2.3
		20 mg/d	3.6
		Placebo	7.1
Caplehorn	238	>80 mg/d	0.3
		60-80 mg/d	0.8
		<60 mg/d	2.1

Evidence-Based Practices:

Elements to Maximize OAT Outcomes

- ***Adequate*** Methadone Dose
- Availability of counseling
- Maintenance versus abstinence/detoxification program orientation
- Contingency management with focus on positive and immediate reinforcement/rewards

Source: Opioid Agonist Therapy Monitoring System (OMS) Willenbring et al. 2003

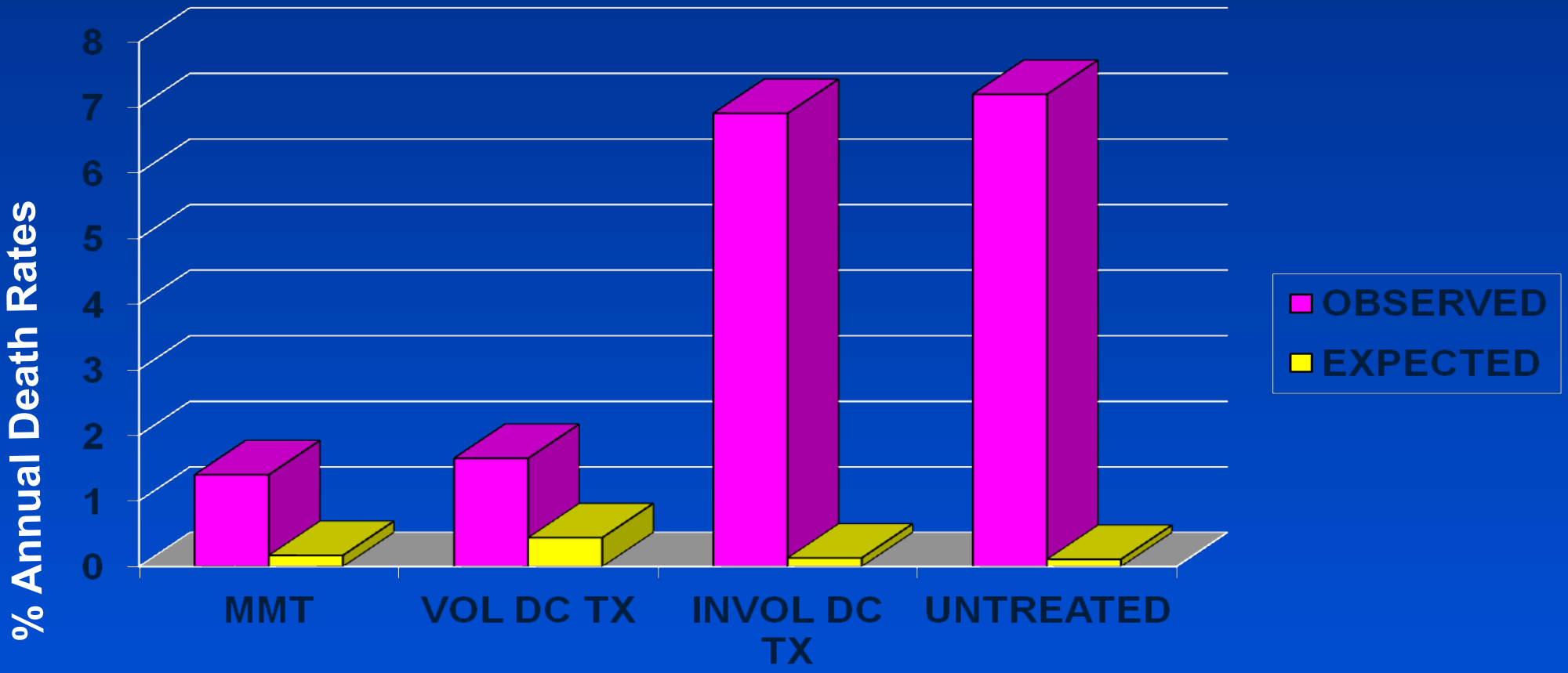
What Does OMT DO?

Impact of Treatment!

Impact of Maintenance Treatment

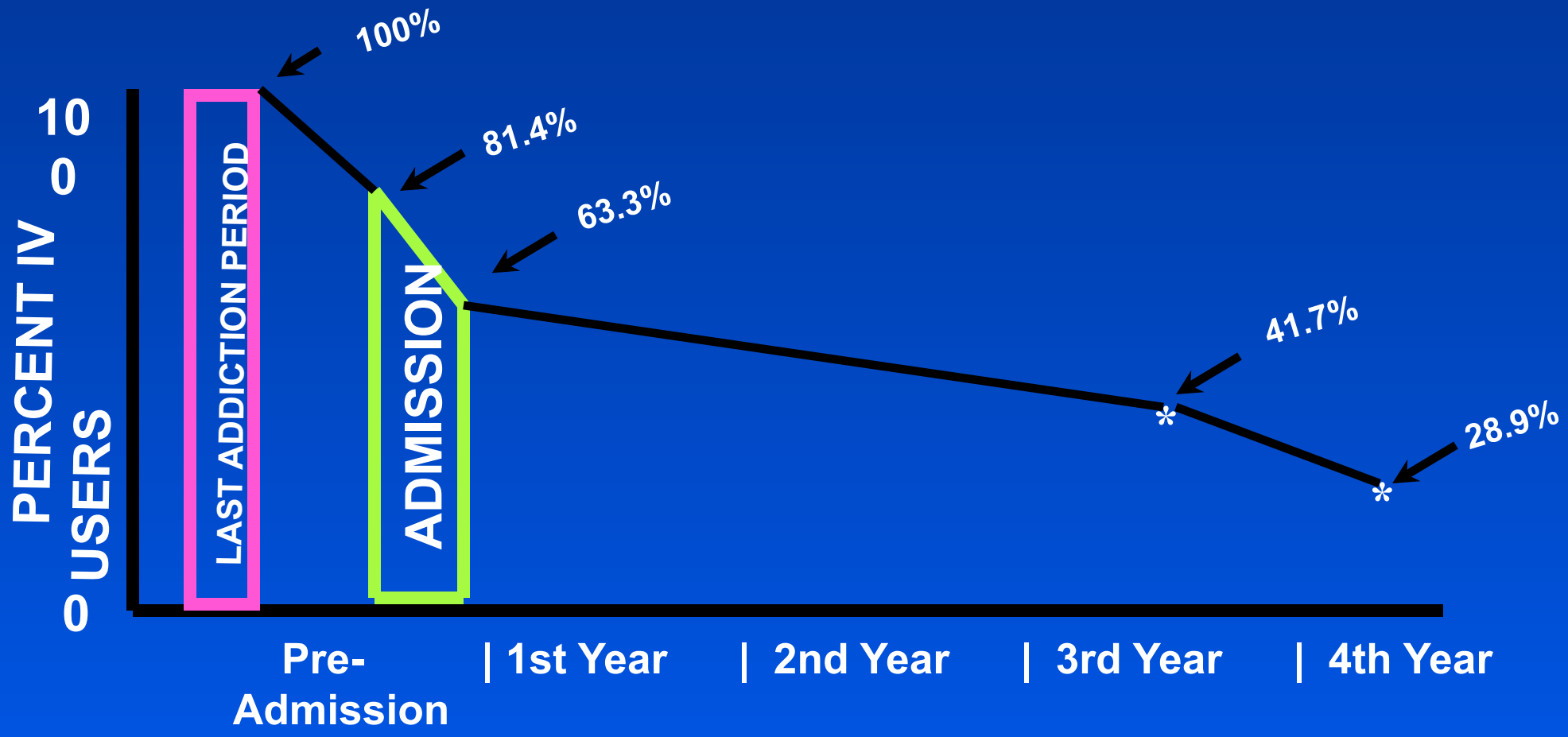
- Reduction death rates (Grondblah, ‘90)
- Reduction IVDU (Ball & Ross, ‘91)
- Reduction crime days (Ball & Ross)
- Reduction rate of HIV seroconversion
  (Bourne, ‘88; Novick ‘90,; Metzger ‘93)
- Reduction relapse to IVDU (Ball & Ross)
- Improved employment, health, & social function

DEATH RATES IN TREATED AND UNTREATED HEROIN ADDICTS



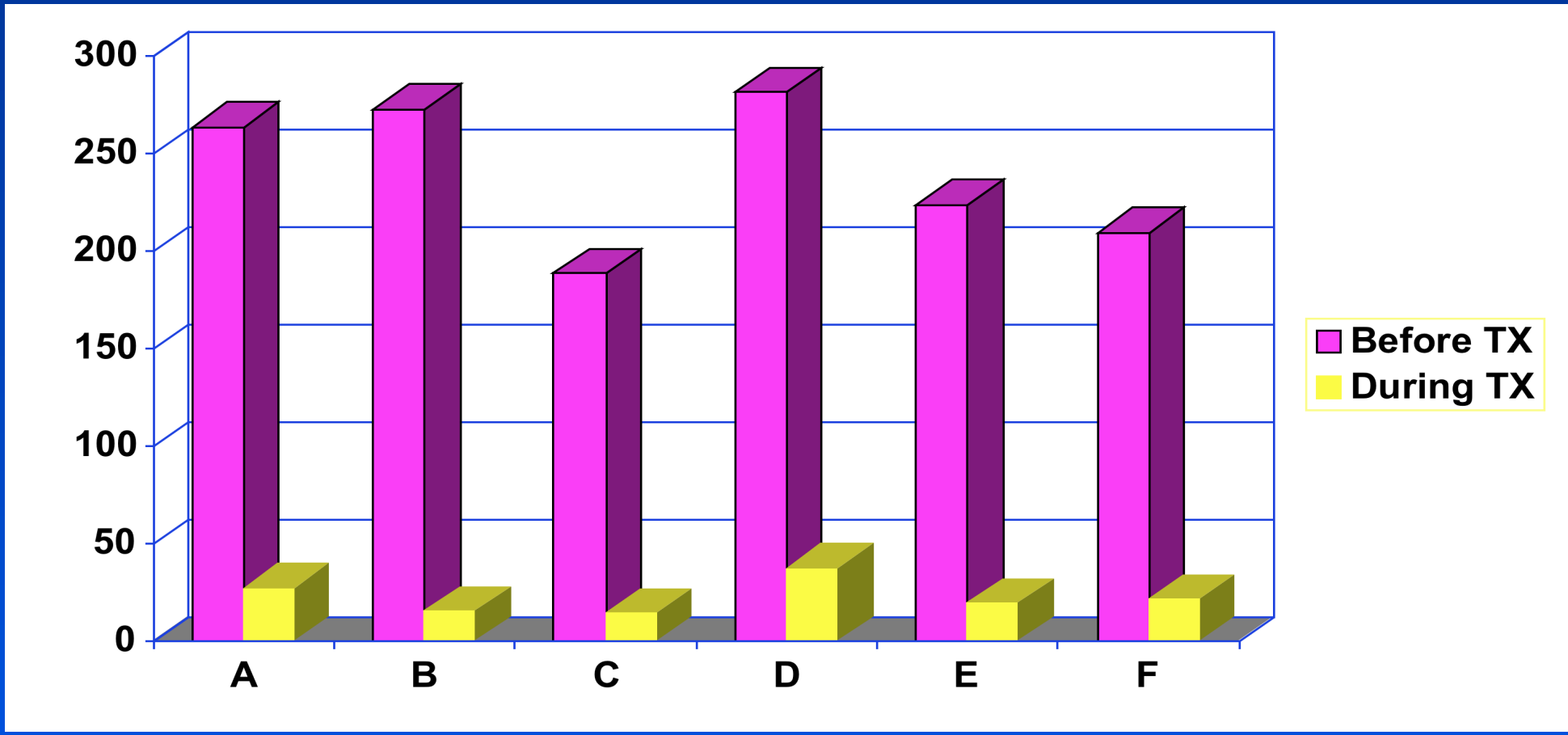
Slide data courtesy of Frank Vocci, MD, NIDA - Reference: Grondblah, L. et al. ACTA PSCHIATR SCAND, P. 223-227, 1990

Impact of MMT on IV Drug Use for 388 Male MMT Patients in 6 Programs



Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991

Crime among 491 patients before and during MMT at 6 programs



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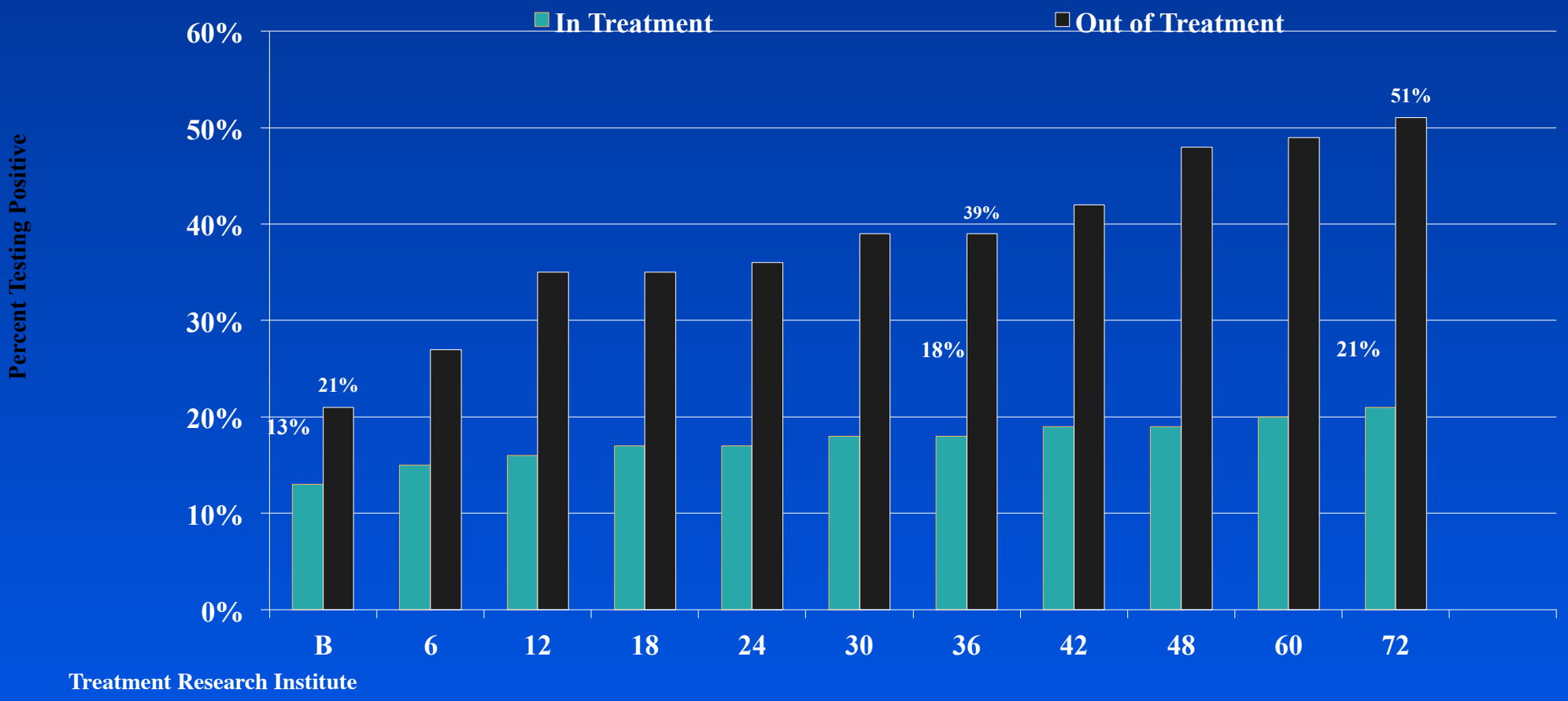
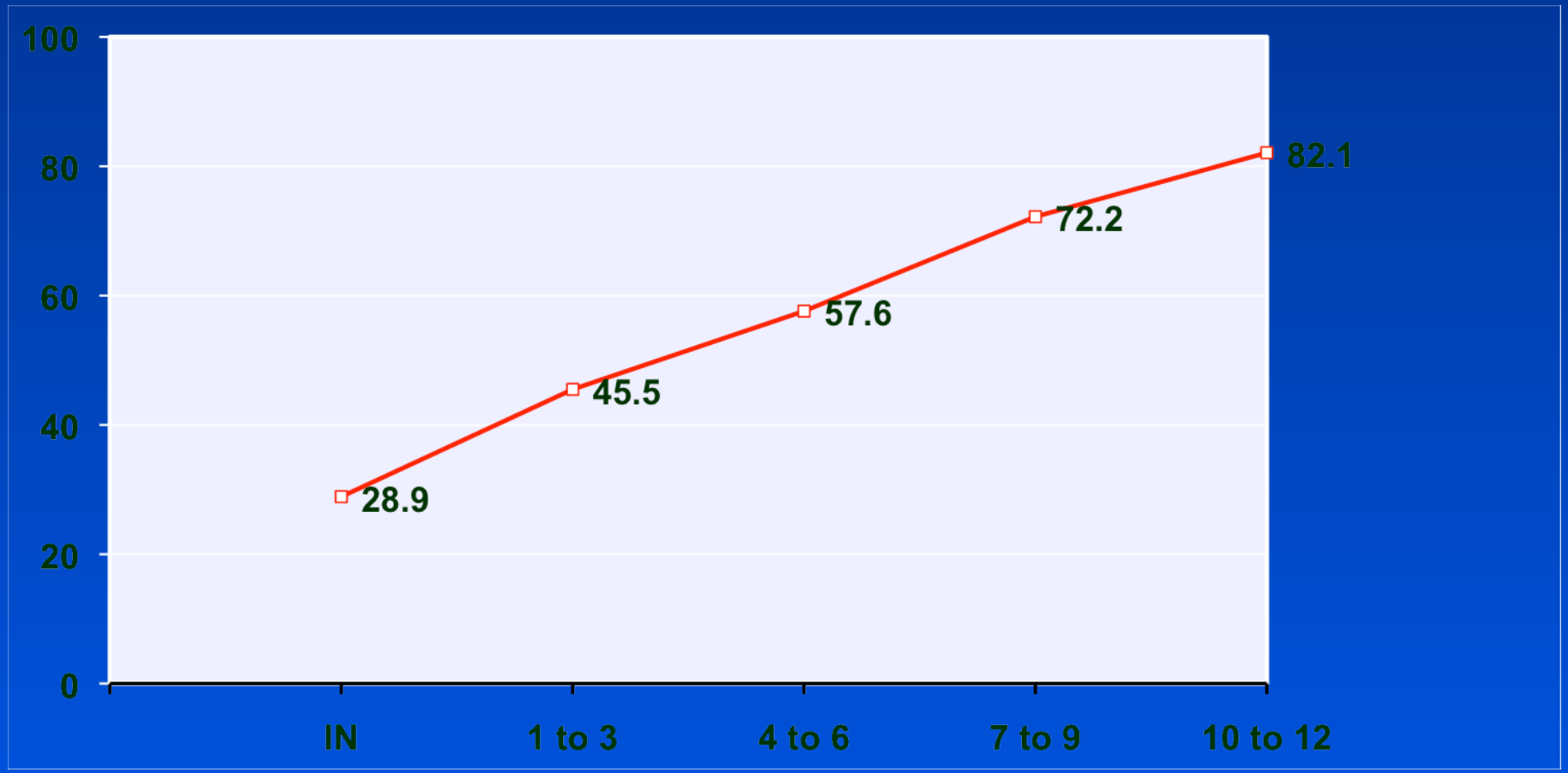
HIV Infection Rates by Treatment Status at Time of Enrollment



Treatment Research Institute

Relapse to IV drug use after MMT
105 male patients who left treatment



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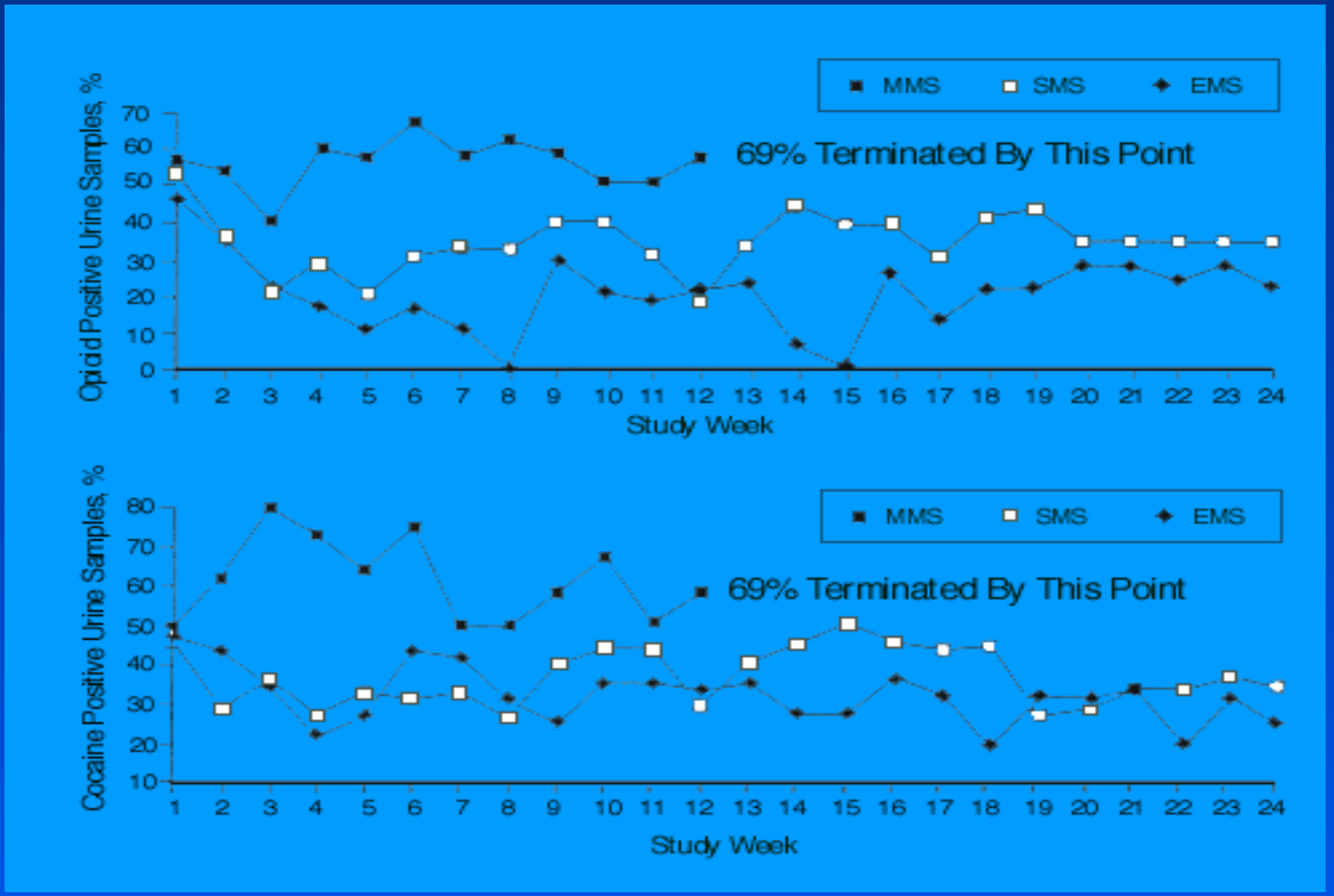
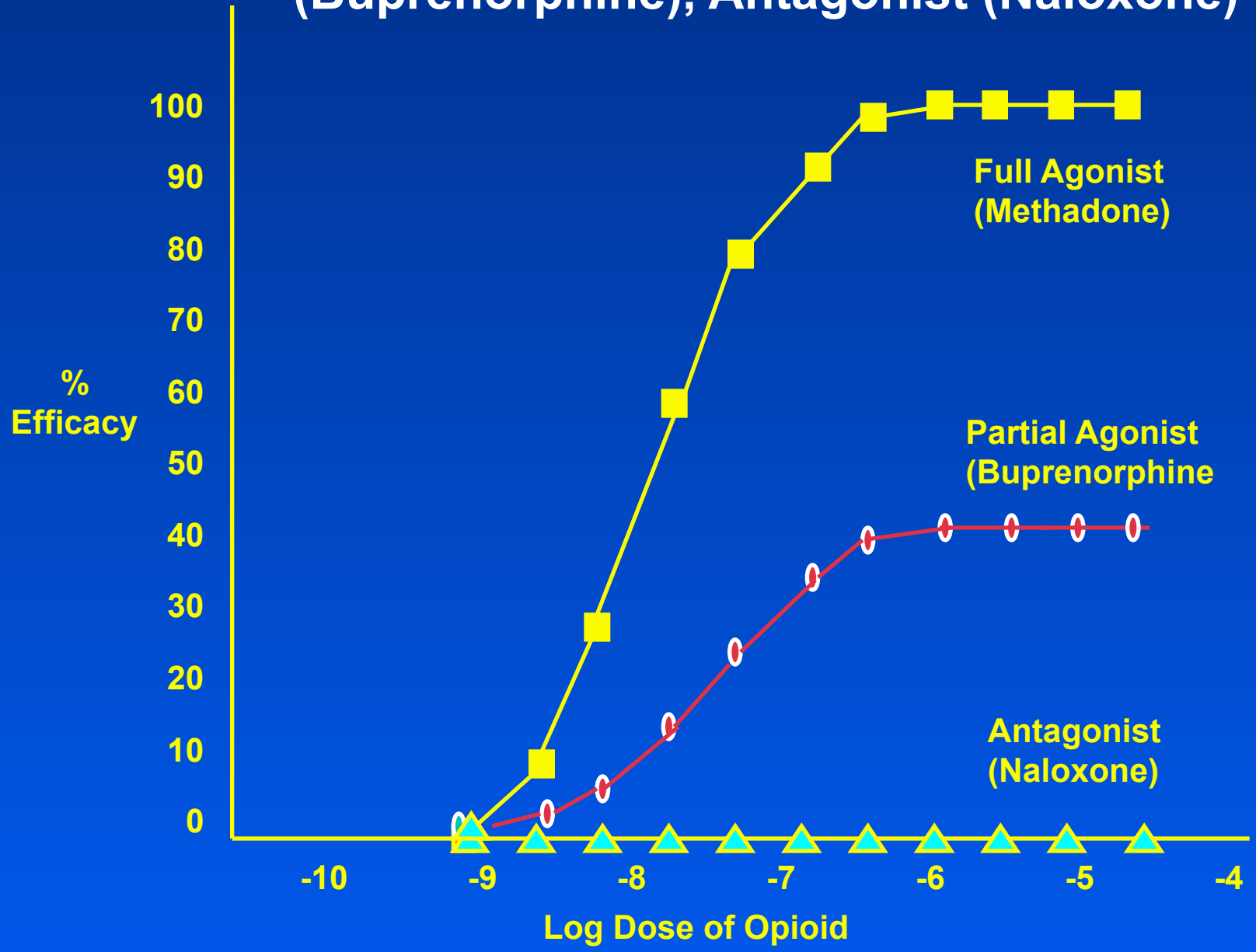


McLellan, et al, 1993

Other Pharmacotherapies for Maintenance Treatment of Opioid Dependence: Buprenorphine, Buprenorphine/Naloxone and Naltrexone

Buprenorphine and Buprenorphine/Naloxone

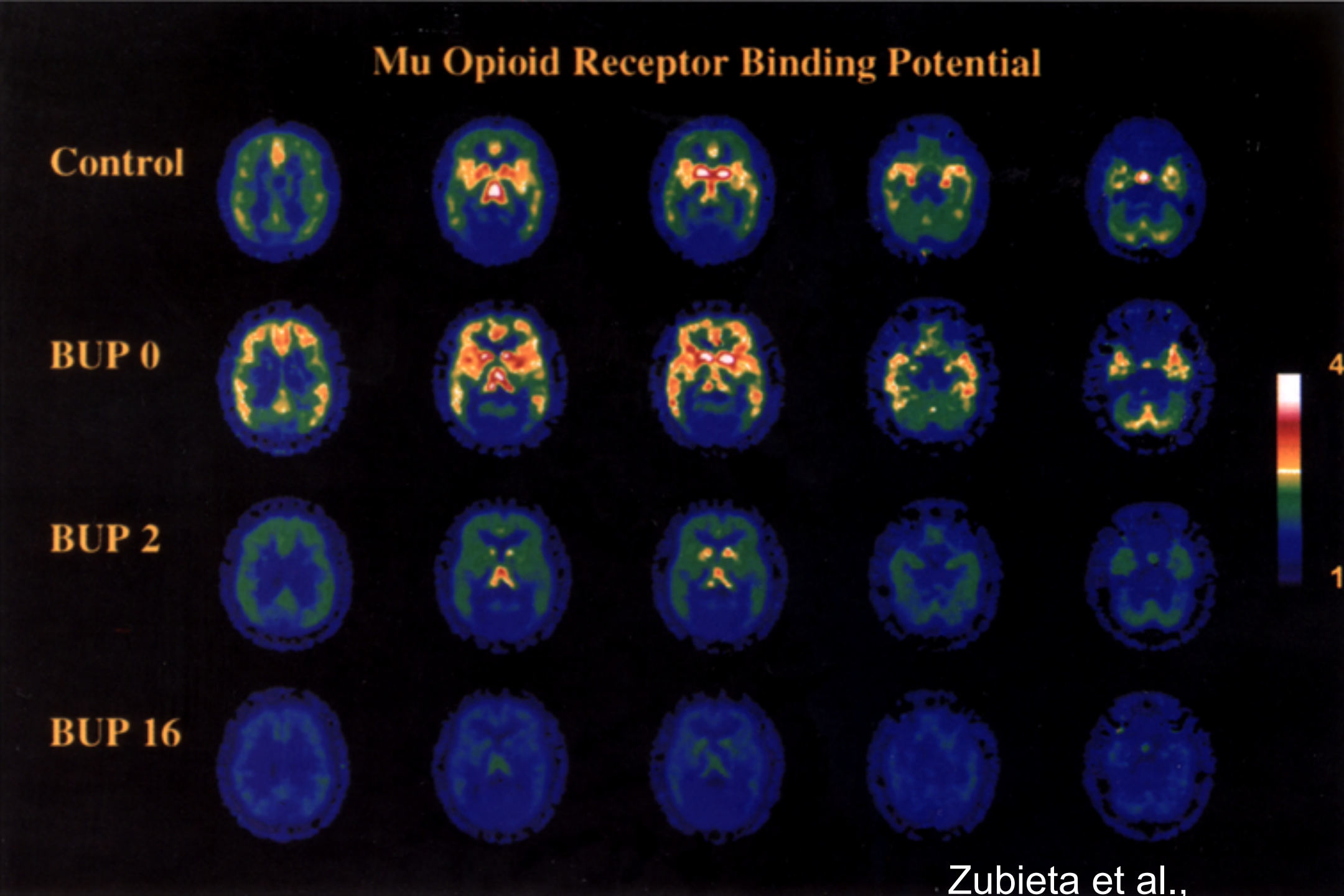
Intrinsic Activity: Full Agonist (Methadone), Partial Agonist (Buprenorphine), Antagonist (Naloxone)



Affinity and Dissociation

Buprenorphine has:

- high affinity for mu opioid receptor –
  - competes with other opioids and blocks their effects
- slow dissociation from mu opioid receptor –
  - prolonged therapeutic effect for opioid dependence treatment


Mu Opioid Receptor Binding Potential
Control
BUP 0
BUP 2
BUP 16
4
1
Zubieta et al.,

Potential for Physical Dependence

Repeated administration of buprenorphine produces or maintains physical dependence

However, degree of physical dependence is less than that produced by full agonist opioids

This means withdrawal syndrome should be less severe for buprenorphine

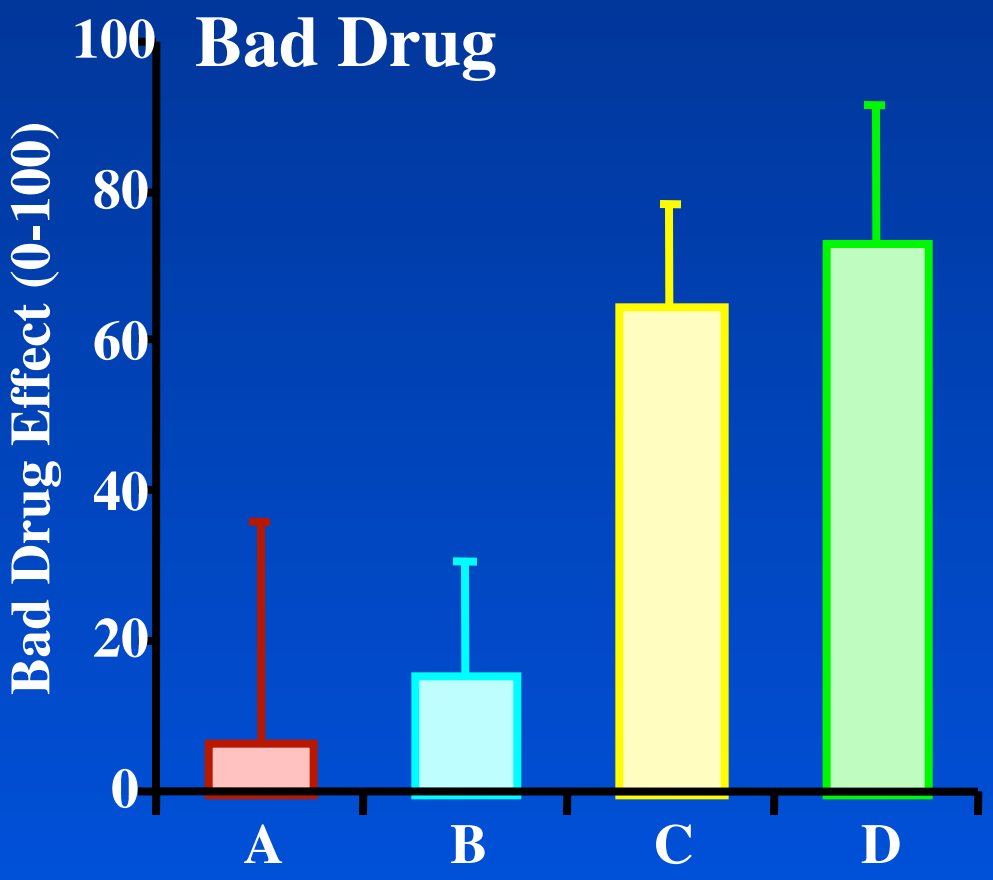
Rationale for Buprenorphine/naloxone

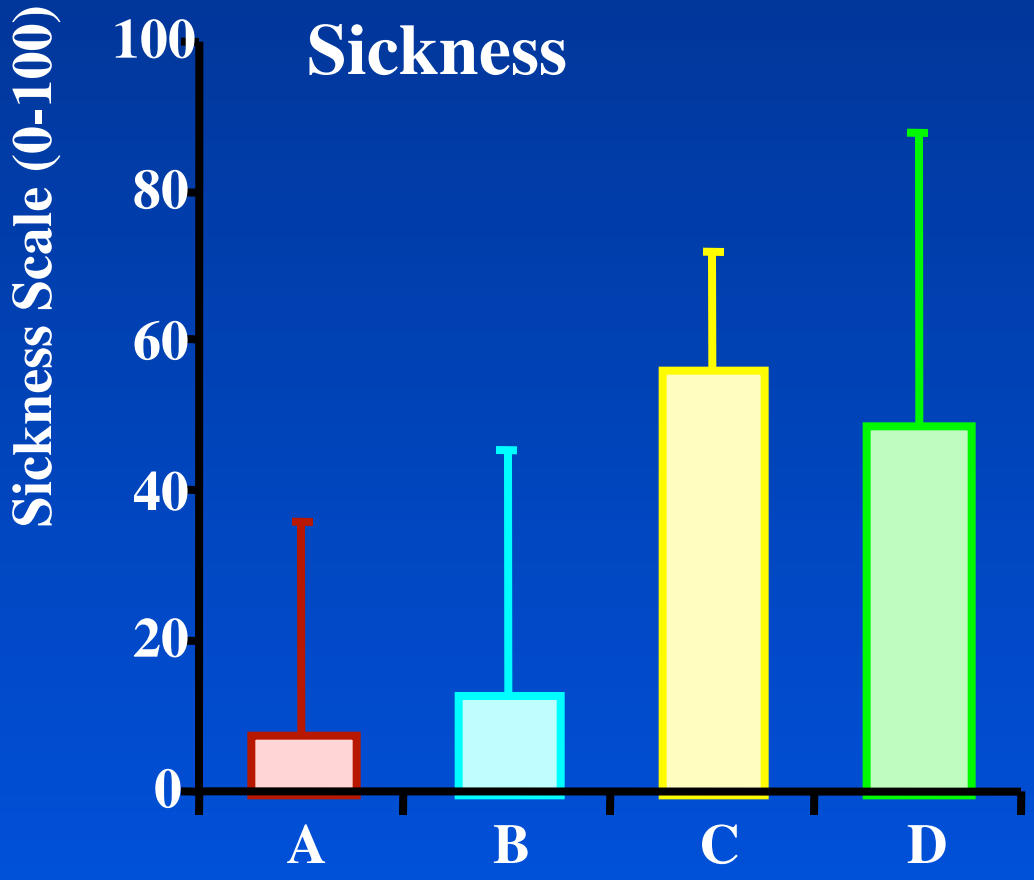
- When taken sublingually
  - Buprenorphine will be well absorbed
  - Naloxone absorption will be minimal
- If taken intravenously
  - Naloxone 100% bioavailable
  - Precipitated withdrawal occurs in opioid maintained patients

Buprenorphine/naloxone infusion

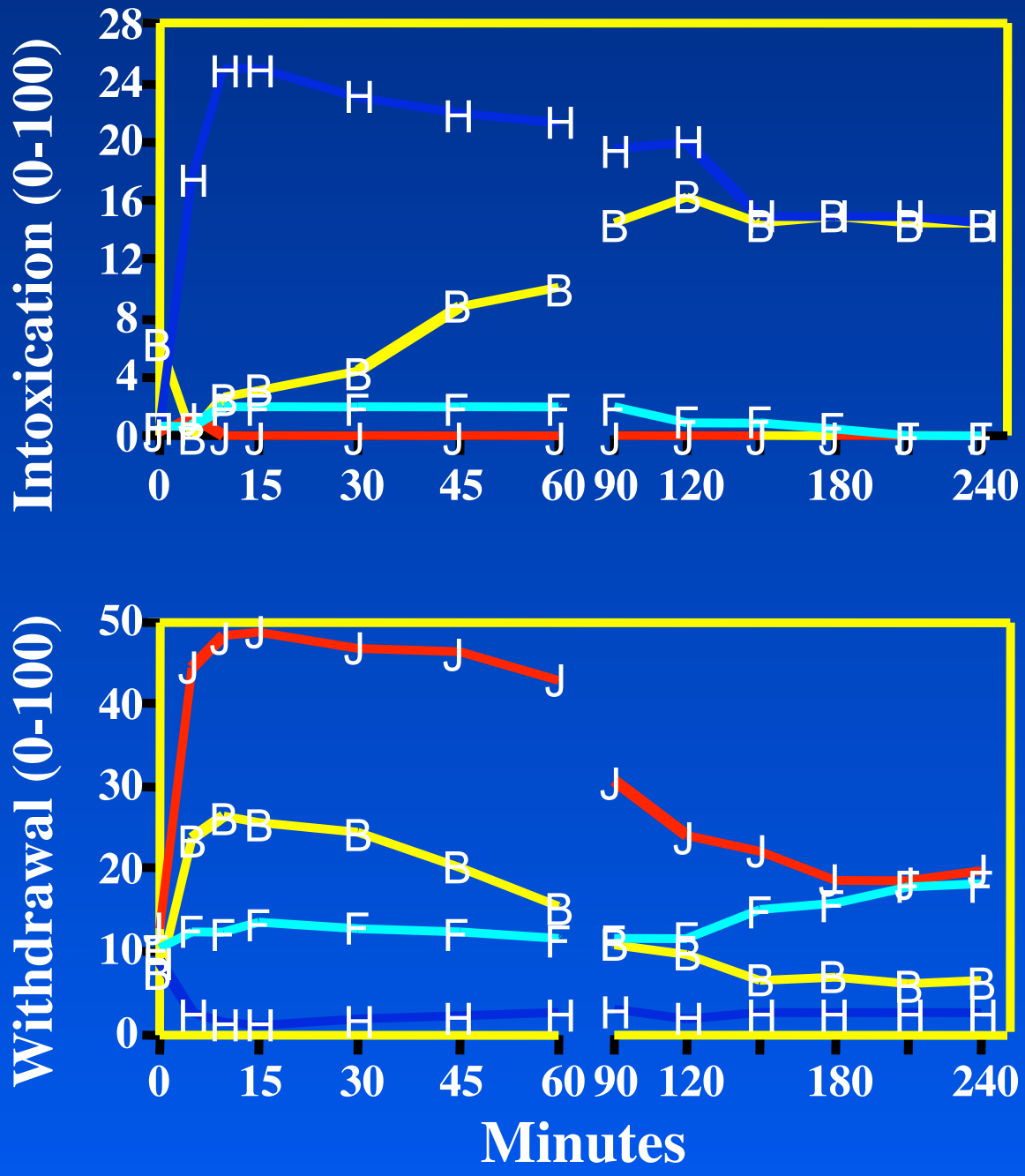
- Study on methadone maintained patients (Mendelson)
- Looked at 6 patients on stable methadone doses of 45 to 60 mg/day
- Challenged IV with
  - Buprenorphine 0.2 mg
  - Naloxone 0.1 mg
  - Buprenorphine 0.2 and Naloxone 0.1 mg
  - Placebo

PEAK EFFECTS – MEAN (±SD)





A Buprenorphine placebo, Naloxone placebo
B Buprenorphine 0.2 mg, Naloxone placebo
C Buprenorphine placebo, Naloxone 0.1 mg
D Buprenorphine 0.2 mg, Naloxone 0.1 mg



B Bup/Nal

J Naloxone

H Buprenorphine

F Placebo

Mean Peak Amount Would Pay for Drug

Bup/Nal	$ 1.90 ± 3.70
Naloxone	0.00 ± 0.00
Buprenorphine	11.90 ± 7.00
Placebo	0.00 ± 0.00

Benzodiazepines and Other Sedating Drugs

- Reports of deaths when buprenorphine injected along with benzodiazepines
  - Reported from France, where tablets available – appears patients dissolve and inject tablets
- Probably possible for this to occur with other sedatives as well

Maintenance Treatment Using Buprenorphine

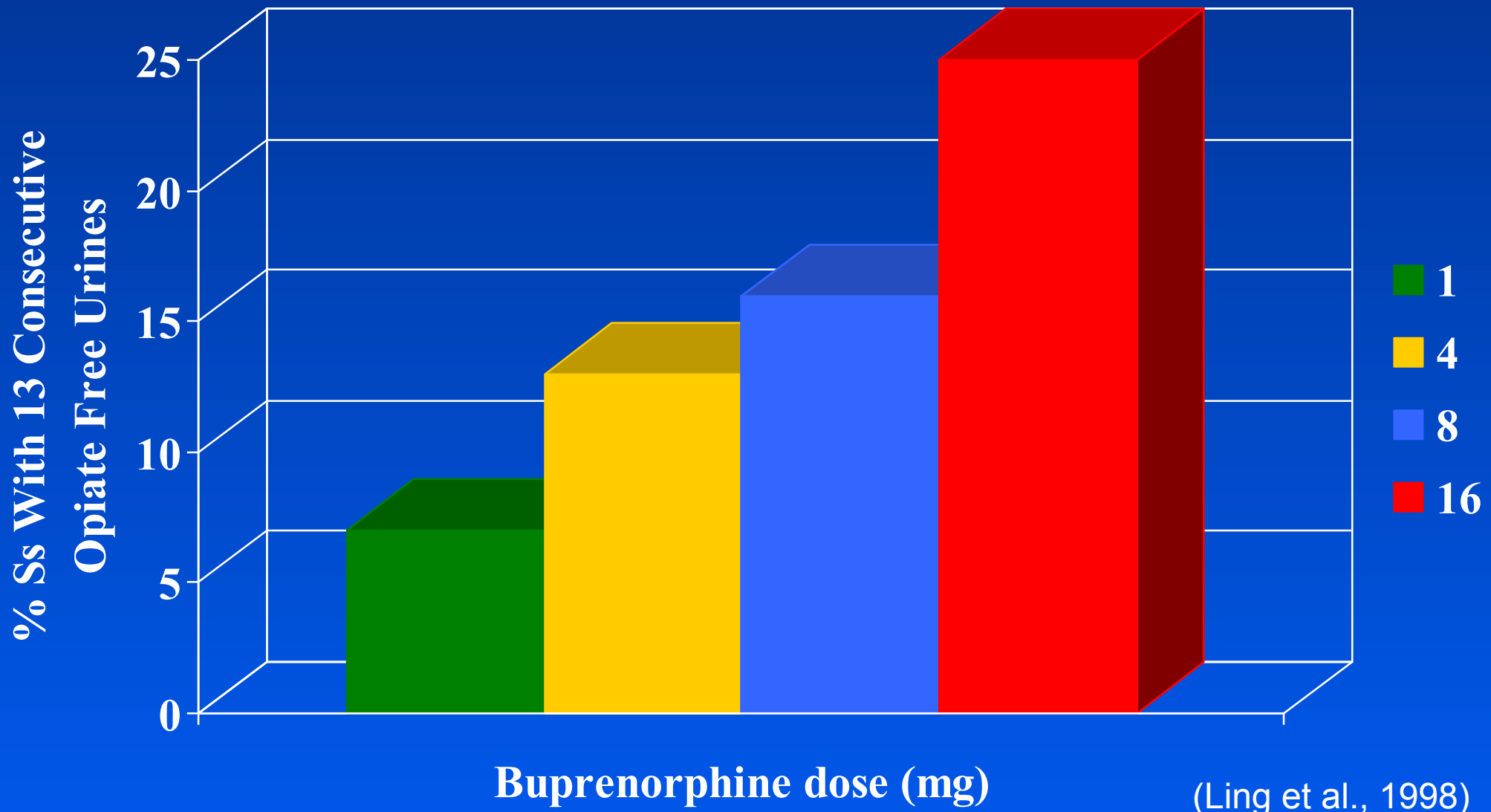
Numerous outpatient clinical trials comparing efficacy of daily buprenorphine to placebo, and to methadone.

Maintenance Treatment Using Buprenorphine

These studies conclude:

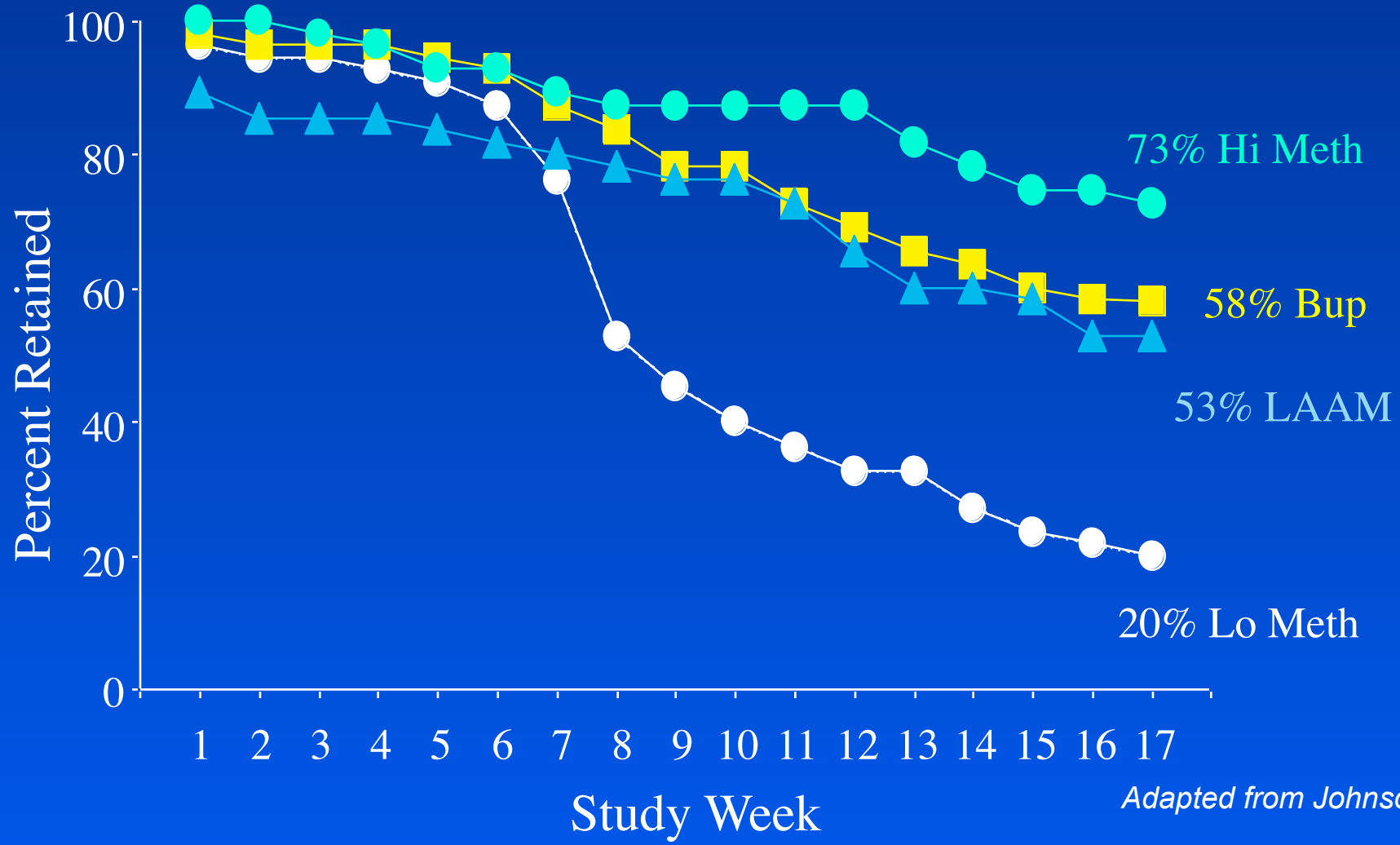
- Buprenorphine more effective than placebo
- Buprenorphine equally effective as moderate doses of methadone (e.g., 60 mg per day)

Different Doses of Buprenorphine: Opiate Use



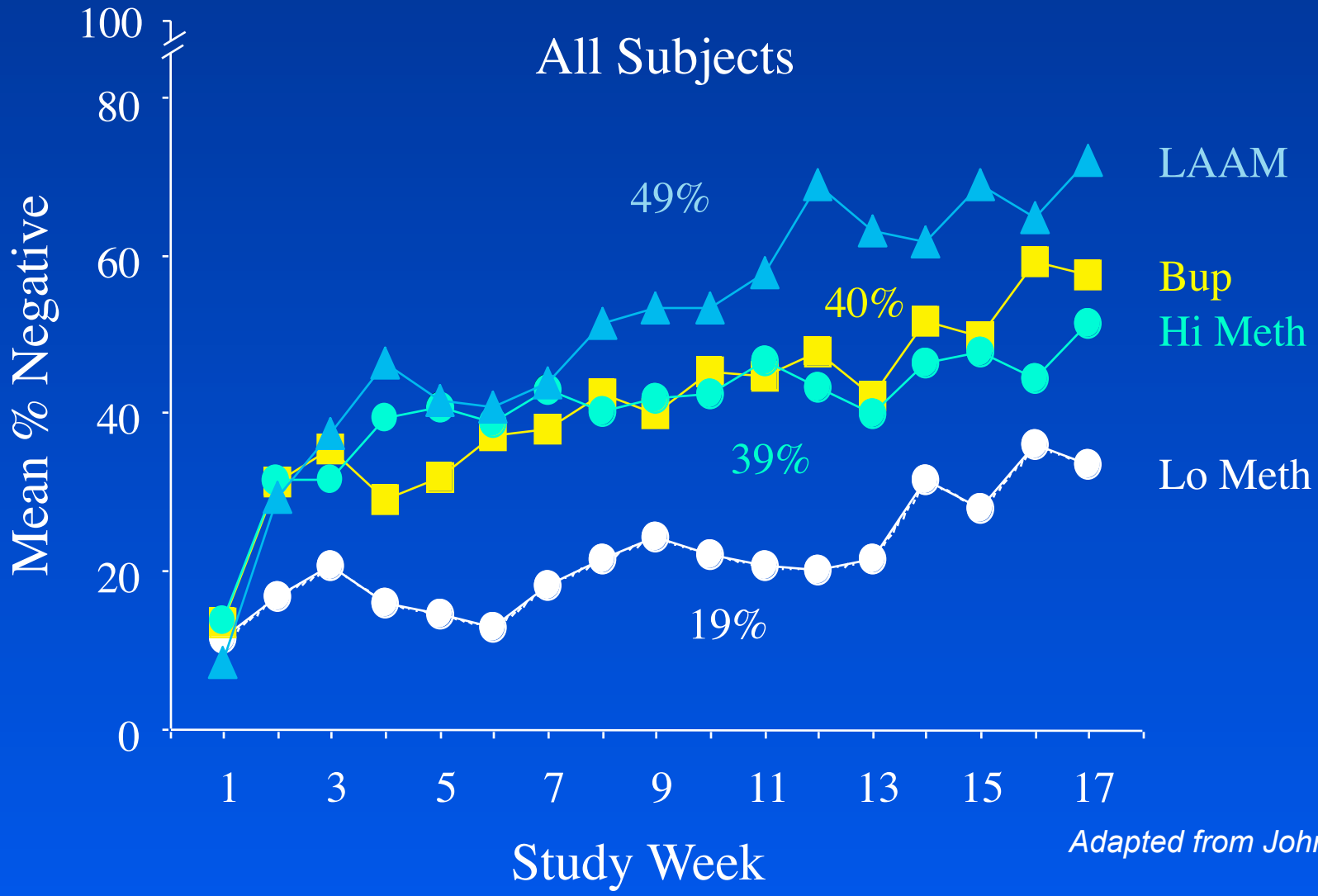
(Ling et al., 1998)

Buprenorphine, Methadone, LAAM: Treatment Retention



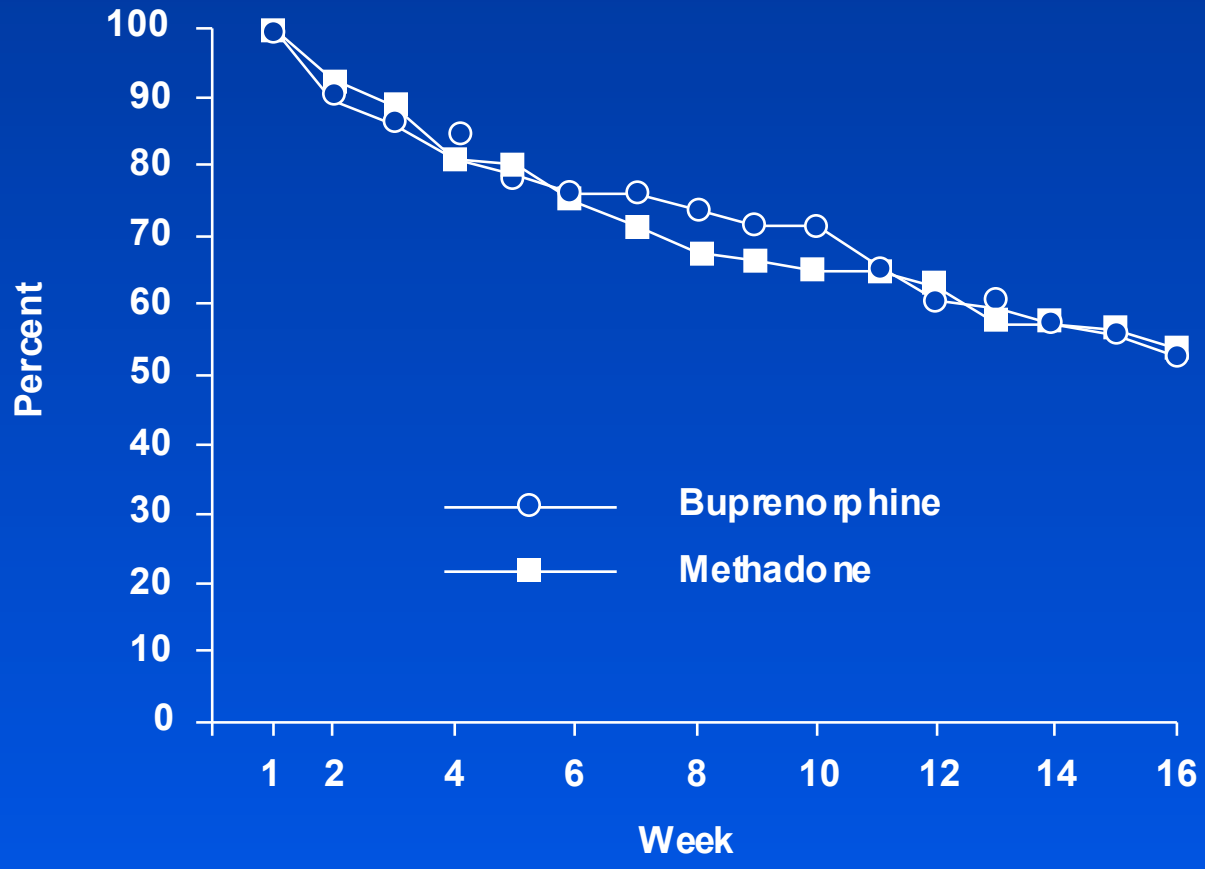
Adapted from Johnson, et al., 2000

Buprenorphine, Methadone, LAAM: Opioid Urine Results



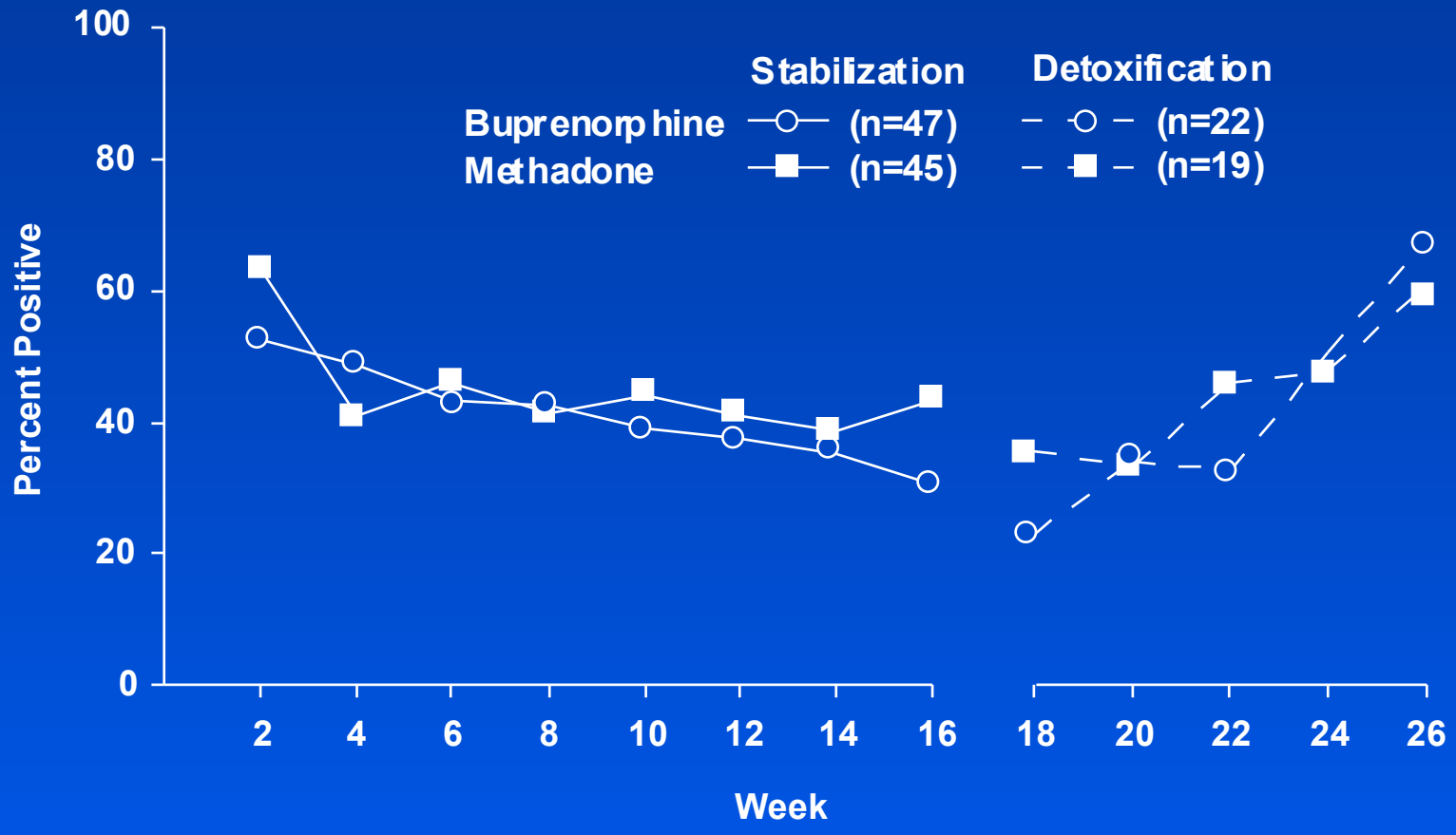
Adapted from Johnson, et al., 2000

Buprenorphine – methadone: treatment retention

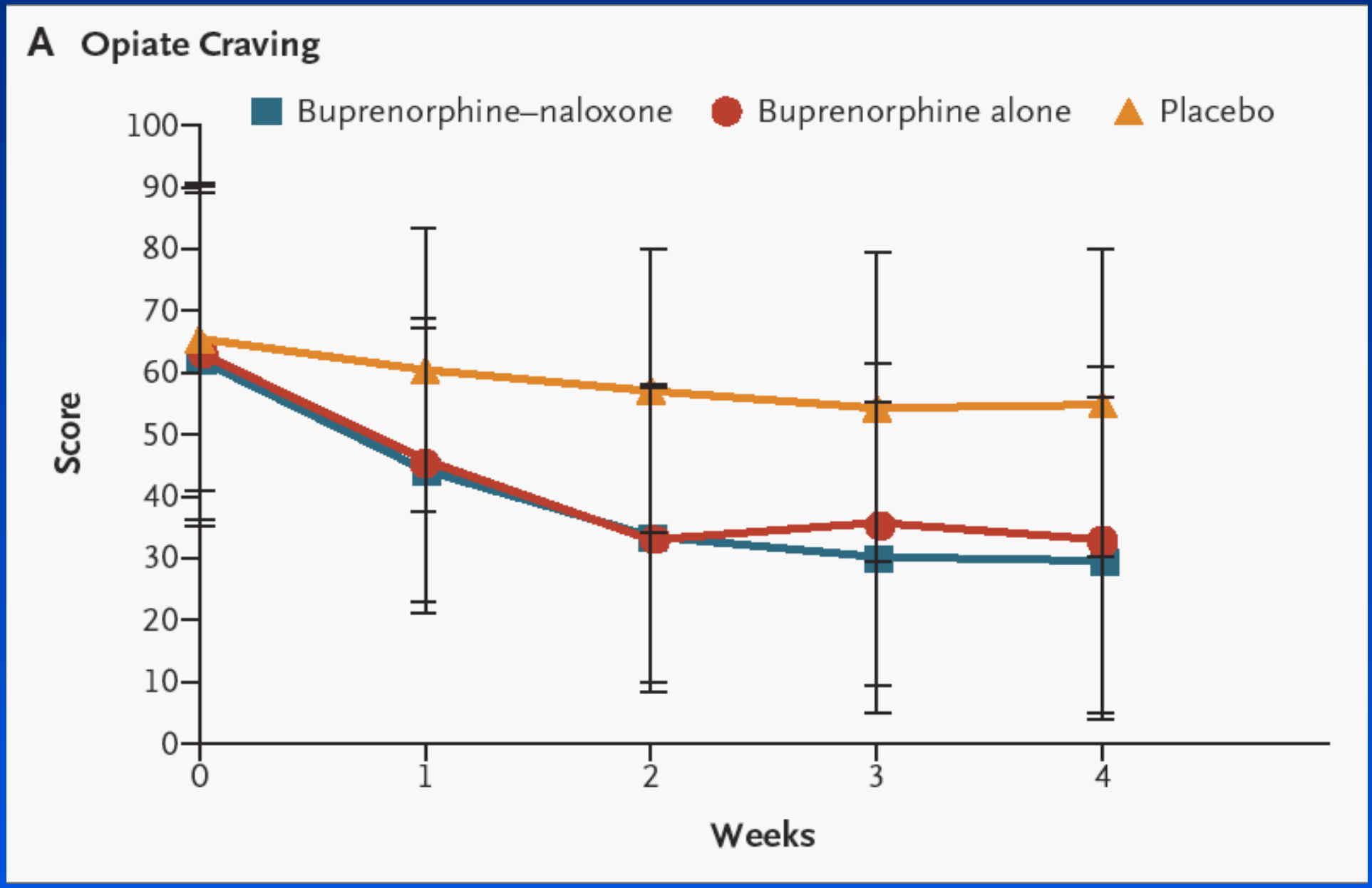


(Strain et al., 1994)

Buprenorphine – methadone: opioid urine results



(Strain et al., 1994)


A Opiate Craving
Buprenorphine–naloxone
Buprenorphine alone
Placebo
Score
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
Weeks

PATIENT SELECTION

Issues related to recommending buprenorphine over methadone:

- Psychiatric co-morbidities
- Substance abuse co-morbidity
  - BZD's and alcohol
- Policy regarding take-home doses
- Finances

POLICY ISSUES

Other policy issues:

- Whether to offer buprenorphine at all
- Patient selection

POLICY ISSUES

What to do if patient refuses physician recommendation of medication?

1. Engage the patient in motivational therapy
2. Educate the patient on the reasons for the decision
3. Offer higher level of care
4. ensure that patient knows the clinic is available if/ when s/he decides to engage at an appropriate level of care

Buprenorphine Maintenance

Once patient has achieved stable dose, determine office schedule.

Normal daily dose is ~14mg/day; little evidence of need for dose greater than 24mg/day.

NO evidence of need for more than once daily dose; patients may prefer more than once daily dose.

Withdrawal Using Buprenorphine

Studies have primarily looked at buprenorphine maintenance, not withdrawal

In general, withdrawal using opioids (e.g., methadone) has had poor outcomes

Results with buprenorphine may be better (may have a milder withdrawal syndrome)

Buprenorphine Maintenance/Withdrawal

- Buprenorphine maintenance vs. withdrawal:
  - Double-blind, random assignment to:
    - 16 mg/day SL buprenorphine tablets, or
    - 6 day buprenorphine withdrawal followed by placebo
  - 20 patients per group
  - Used tablets of buprenorphine, placebo

Kakko et al. 2003

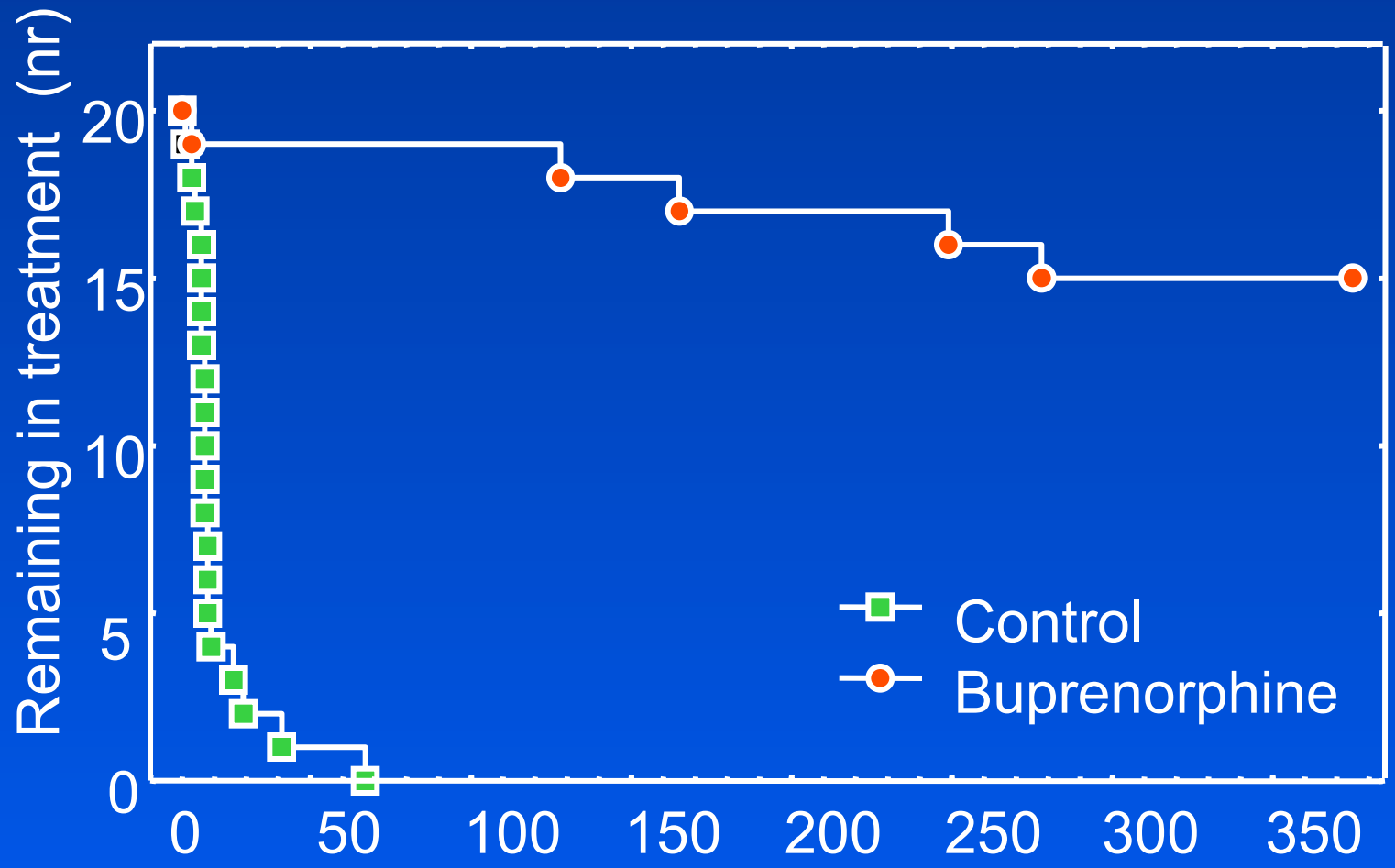
Buprenorphine Maintenance/Withdrawal

- Comparison of buprenorphine maintenance vs. withdrawal:
  - First week of study was inpatient; study lasted one year; take home doses allowed after 6 months of treatment
  - Outcome measures included
    - treatment retention
    - urine samples that were collected under supervision and tested three times per week
    - ASI scores

Buprenorphine Maintenance/Withdrawal

- Comparison of buprenorphine maintenance vs. withdrawal:
  - All participants also received a relatively rich set of psychosocial treatments
    - group and individual counseling
    - assistance with various social service agencies (for example, for housing and employment)

Buprenorphine Maintenance/Withdrawal: Retention



(Kakko et al., 2003)

Buprenorphine Maintenance/Withdrawal: Mortality

	Placebo	Buprenorphine	Cox Regression
Dead	4/20 (20%)	0/20 (0%)	X^2=5.9; p=0.015

(Kakko et al, 2003)

Summary

Buprenorphine/naloxone and buprenorphine are safe and and highly effective in treating opioid dependence.

Buprenorphine can be effectively utilized in OTPs and in office-based practice to assist opioid-dependent patients.

Physicians and allied health personnel need to understand the complex pharmacology of buprenorphine in order to use it effectively for their patient's good.

Naltrexone

Naltrexone Injectable

- 2 Groups of patients are appropriate for use of naltrexone injectable:
  - Patients entering treatment in active addiction OR after short-term detoxification/rehabilitation
  - Patients who have succeeded on methadone or buprenorphine and successfully tapered off agonist medication

Naltrexone Injectab;e Use for Opioid Dependence

Unintended precipitation of opioid withdrawal

To prevent occurrence of an acute abstinence syndrome (withdrawal) in patients dependent on opioids, or exacerbation of a preexisting subclinical abstinence syndrome:

- Patients must be opioid free for a minimum of 7-10 days before starting VIVITROL treatment
- Patients must be free of all opioid-containing medications, including medications used to treat opioid dependence (eg, methadone, buprenorphine and buprenorphne/naloxone)

Naltrexone Injectable - Use for Opioid Dependence
Naloxone Challenge

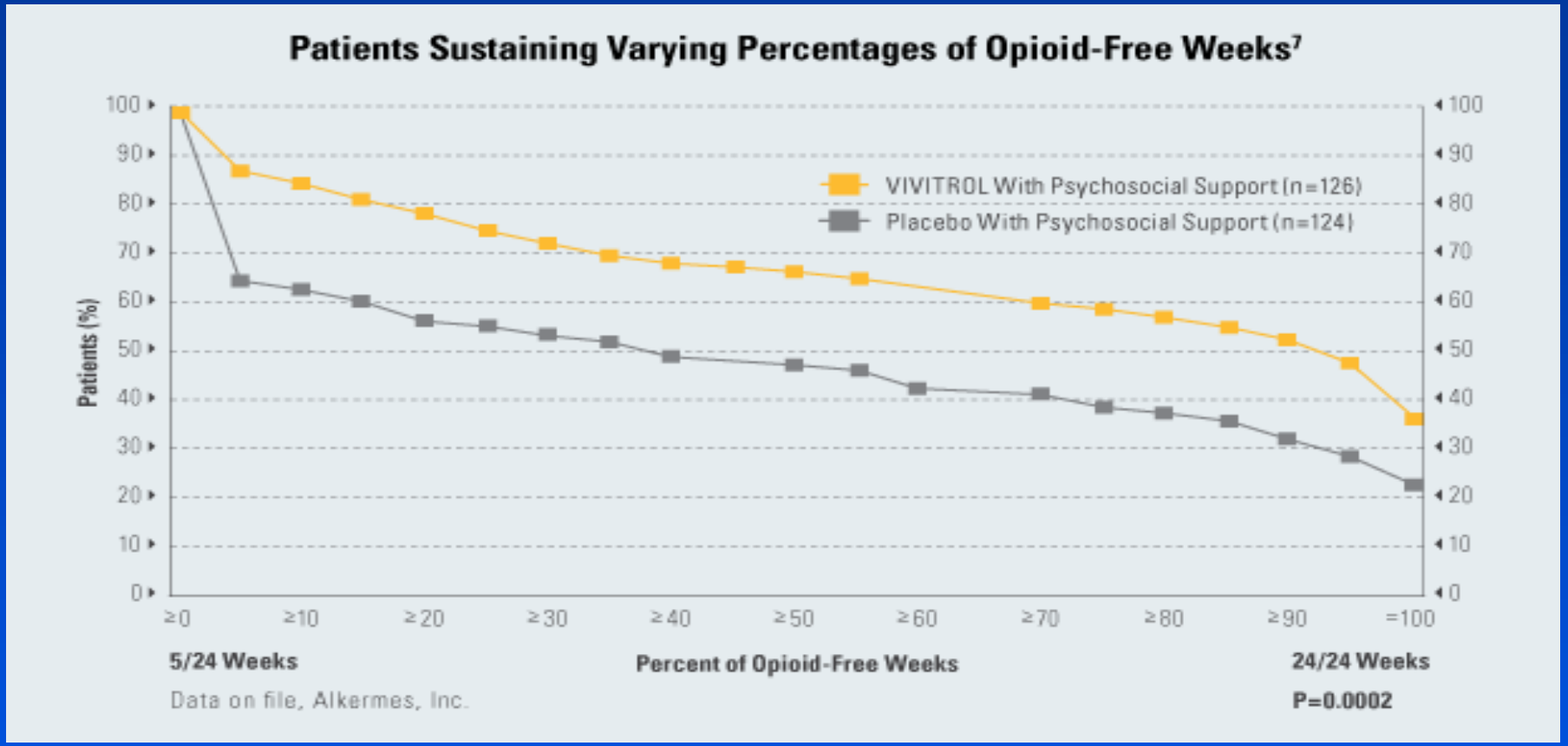
The absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid free:

A naloxone challenge test should be given if the prescribing physician feels there is risk of precipitating a withdrawal reaction following administration of VIVITROL

Naltrexone Injectable

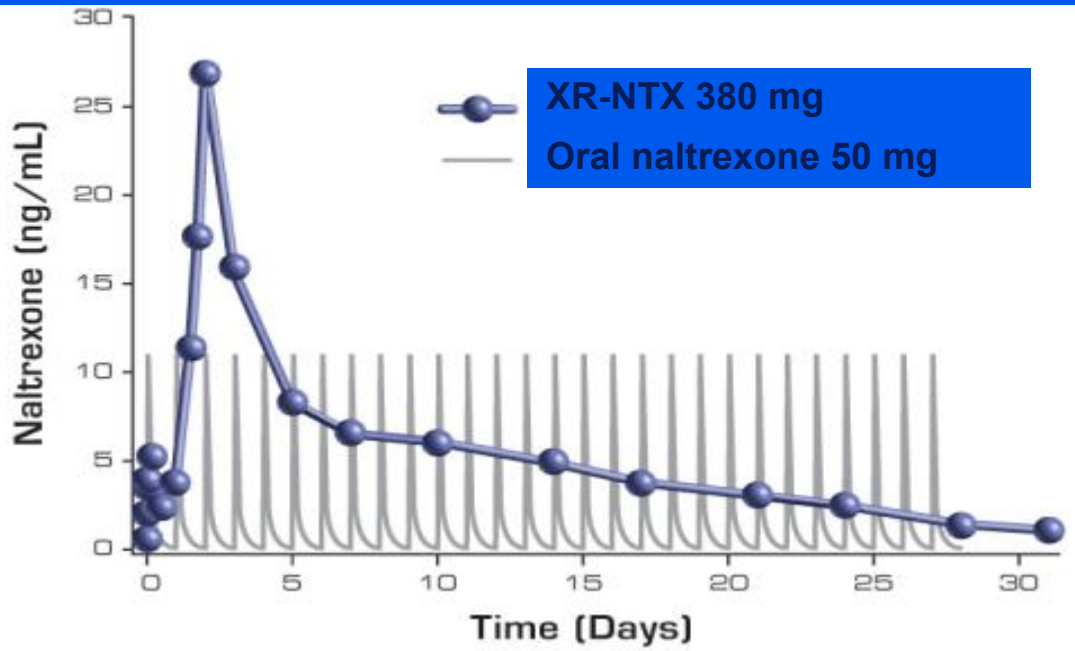
- †The efficacy of naltrexone injectable in the treatment of opioid dependence was evaluated in a 24 week, placebo-controlled, multi-center, double-blind, randomized trial of opioid-dependent (DSM-IV) outpatients, who were completing or had recently completed detoxification. Subjects were treated with an injection every 4 weeks of naltrexone injectble 380 mg or placebo. Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Standardized, manual-based psychosocial support was provided on a biweekly basis to all subjects in addition to medication.

Naltrexone Injectable Efficacy for Opioid Dependence



Pharmacokinetics

Mean steady-state naltrexone concentration following monthly XR-NTX 380 mg compared to daily oral dosing



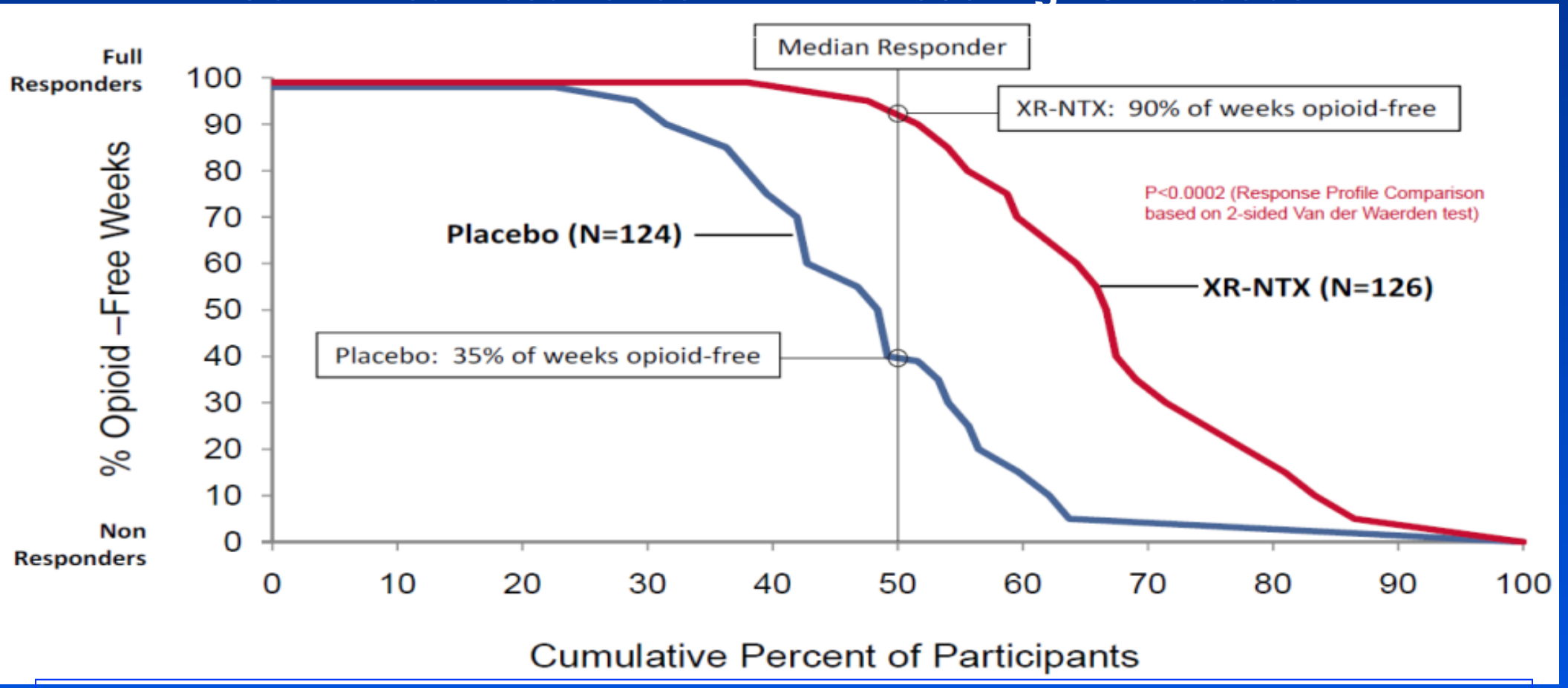
Dean RL. *Front Biosci*. 2005 Jan 1;10:643-655.
Dunbar JL, et al. *Alc Clin Exp Res.* 2006;30:480-490.
Data on File, Alkermes, Inc.

Naltrexone Injectable

- Steady state by 2nd dose
- Minimal accumulation 6β-naltrexol
- Limited 1st pass metabolism by liver
- Monthly naltrexone (380 mg vs 1,500 mg)

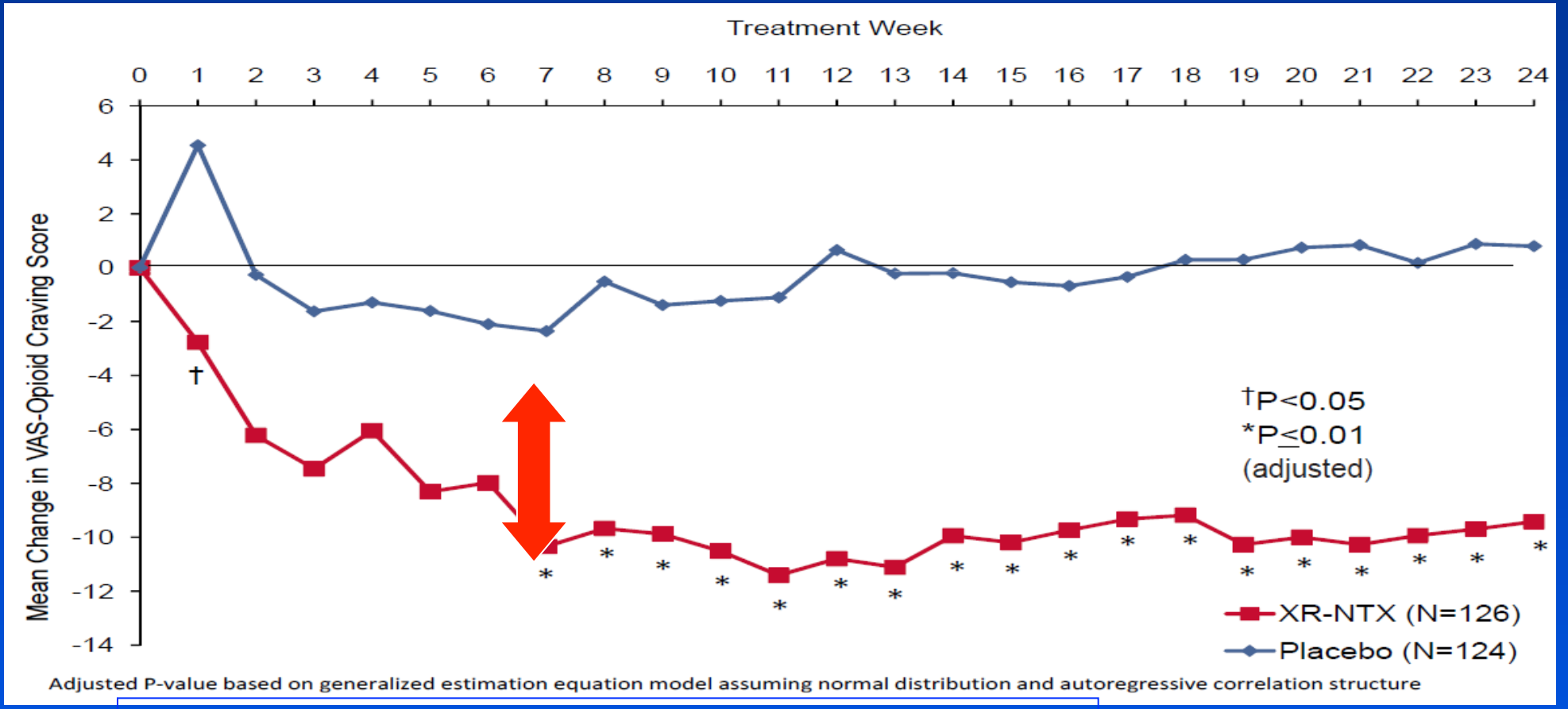
Response Profile

Cumulative % of Participants at Each Rate of Weekly Confirmed Abstinence: XR-NTX 380 mg *vs.* Placebo



- Total abstinence (100% opioid-free weeks) during Weeks 5-24 was reported in 45 (35.7%) of subjects in the XR-NTX group versus 28 (22.6%) subjects in placebo group (P=0.0224).

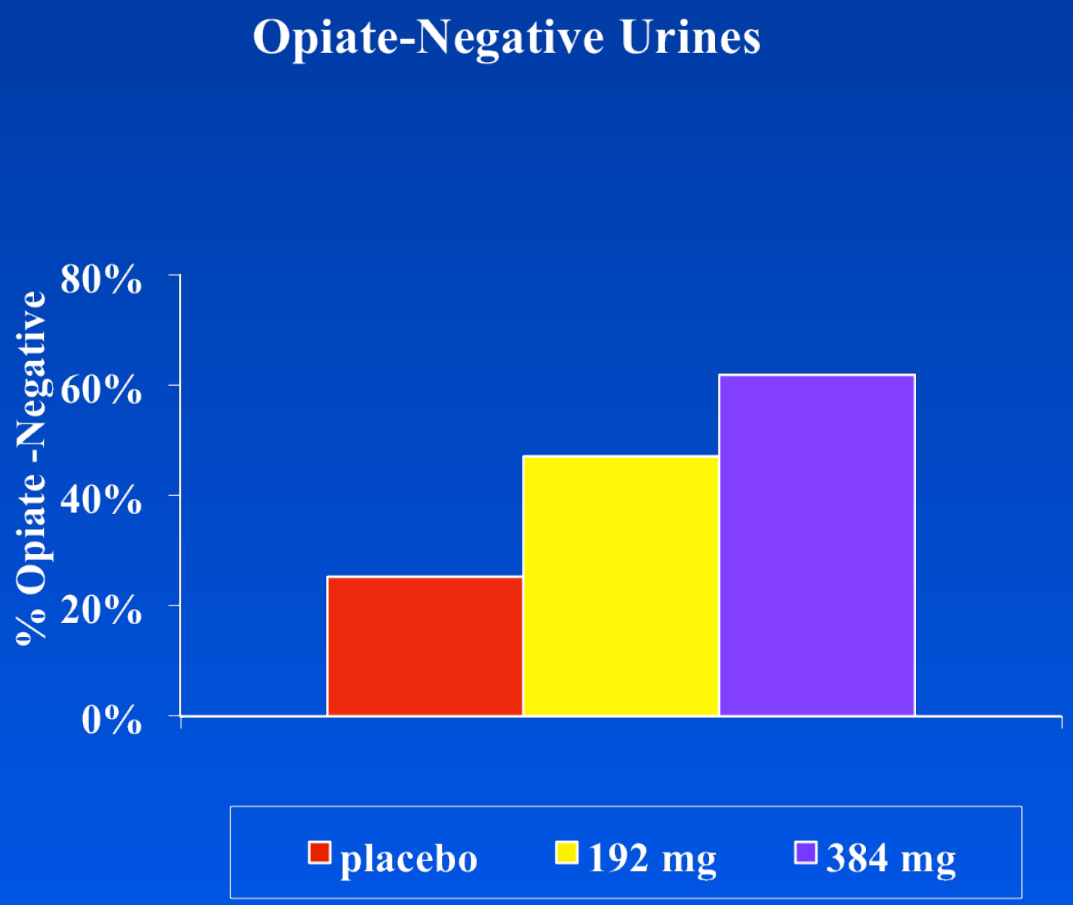
Mean Change From Baseline in VAS-Opioid Craving Score



- Baseline craving scores: XR-NTX = 18; Placebo = 22
- XR-NTX patients showed a 50% reduction-from-baseline in VAS-craving *vs.* no change for placebo

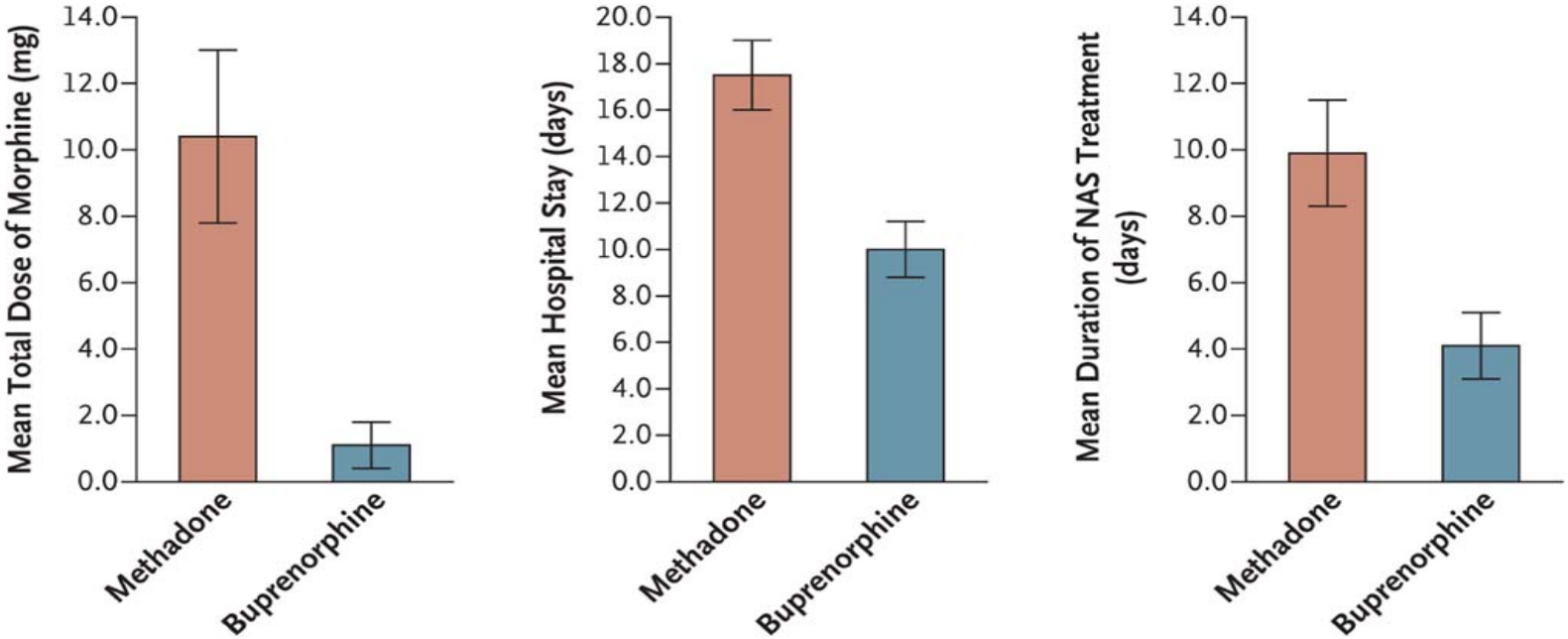
XR naltrexone is effective for heroin users

Extended Release Naltrexone Improves Abstinence



Arch Gen Psychiatry 2006; 63: 210-218

Mean Neonatal Morphine Dose, Length of Neonatal Hospital Stay, and Duration of Treatment for Neonatal Abstinence Syndrome



Jones HE et al. N Engl J Med 2010;363:2320-2331

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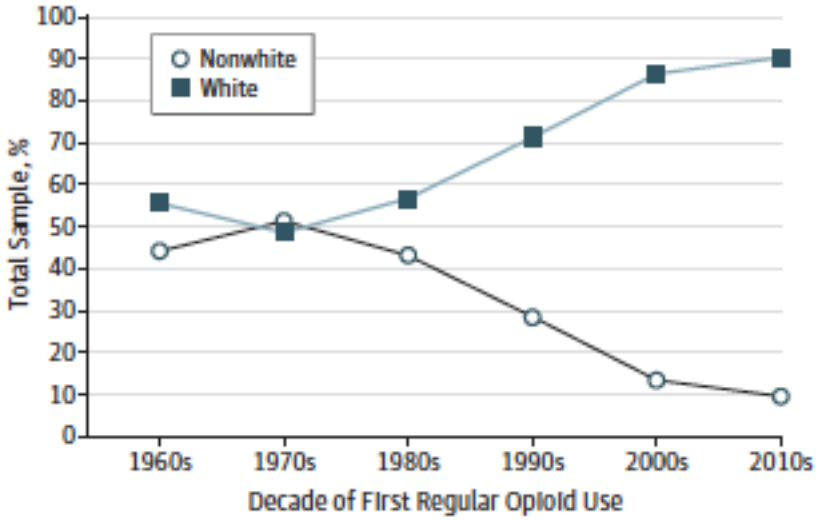
Issues Related to Pregnancy

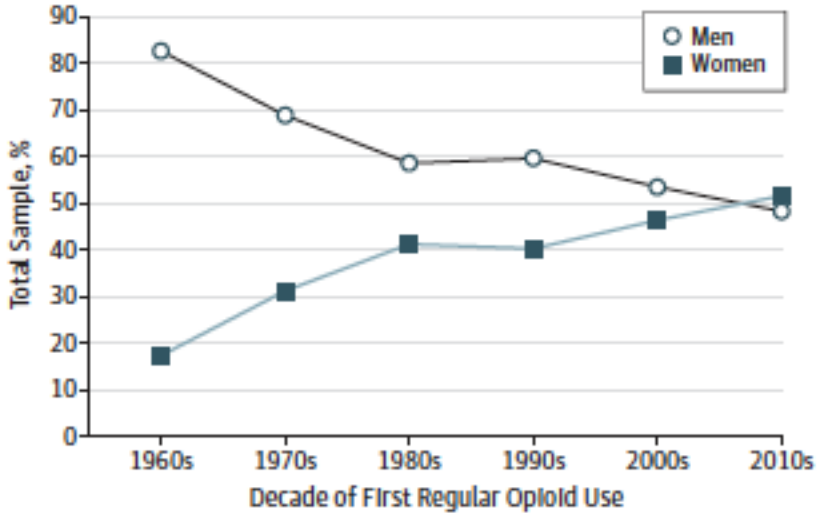
Figure 3. Racial Distribution of Respondents Expressed as Percentage of the Total Sample of Heroin Users



Data are plotted as a function of decade in which respondents initiated their opioid abuse.

Cicero, et al Archives Psychiatry 2014

Figure 2. Sex Distribution of Respondents Expressed as Percentage of the Total Sample



Data are plotted as a function of decade in which respondents initiated their opioid abuse.

Cicero, et al Archives Psychiatry 2014

Methadone as Gold Standard for Pregnant Opiate Addict

- NIH Consensus Panel 1998
- WHO Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence 2009
- CSAT Tip 43
- ASAM/ACOG Opinion of the Committee on Health Care for Underserved Women 2012

Methadone as "Gold Standard" for the Pregnant Opiate Addict

- As evidenced by jails, which do not provide MAT to addicts, do provide methadone for pregnant addicts
- Steady levels of opiates normalize neuroendocrine functioning and prevent fetal distress
- Decreases rates of pregnancy complications, e.g. miscarriage, stillbirth, IUGR, abruptio placenta, hemorrhage, infection
- Improves prenatal care
- Allows for psychosocial interventions to improve level of functioning

Risk-Benefit Comparison of Methadone during Pregnancy

Risks

- Opiate abstinence syndrome in newborn

Benefits

- Protects fetus from repeated withdrawal episodes in utero
- Decreases risk of obstetric and fetal complications
- Decreases IUGR
- Decreases neonatal morbidity and mortality

Risk-Benefit Comparison of Methadone during Pregnancy

- **Benefits**
  - Decreases infections which could be vertically transmitted
  - Decreases opiate and other illicit drug use
  - Decreases criminal activity
  - Improves overall health and well-being

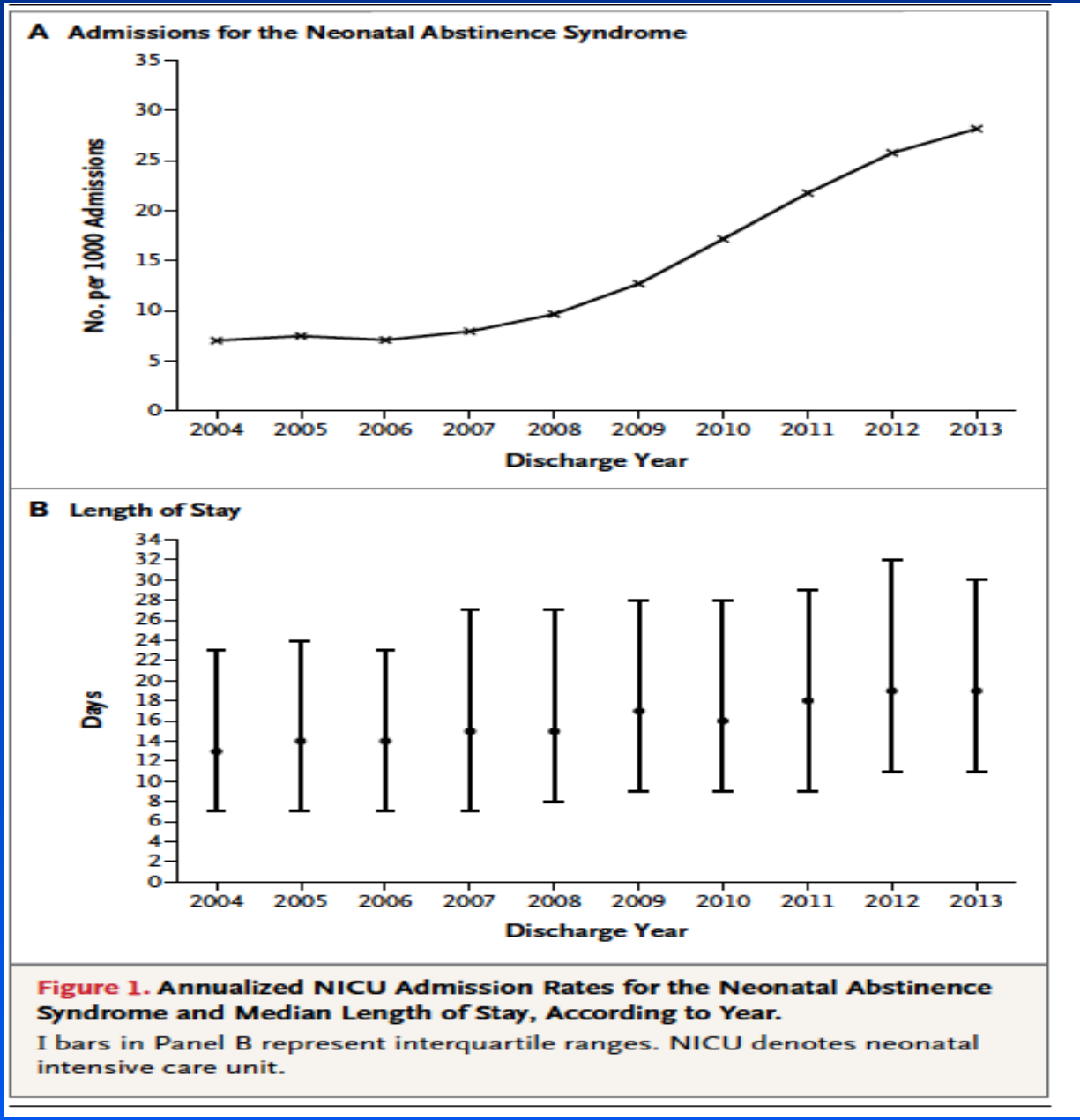
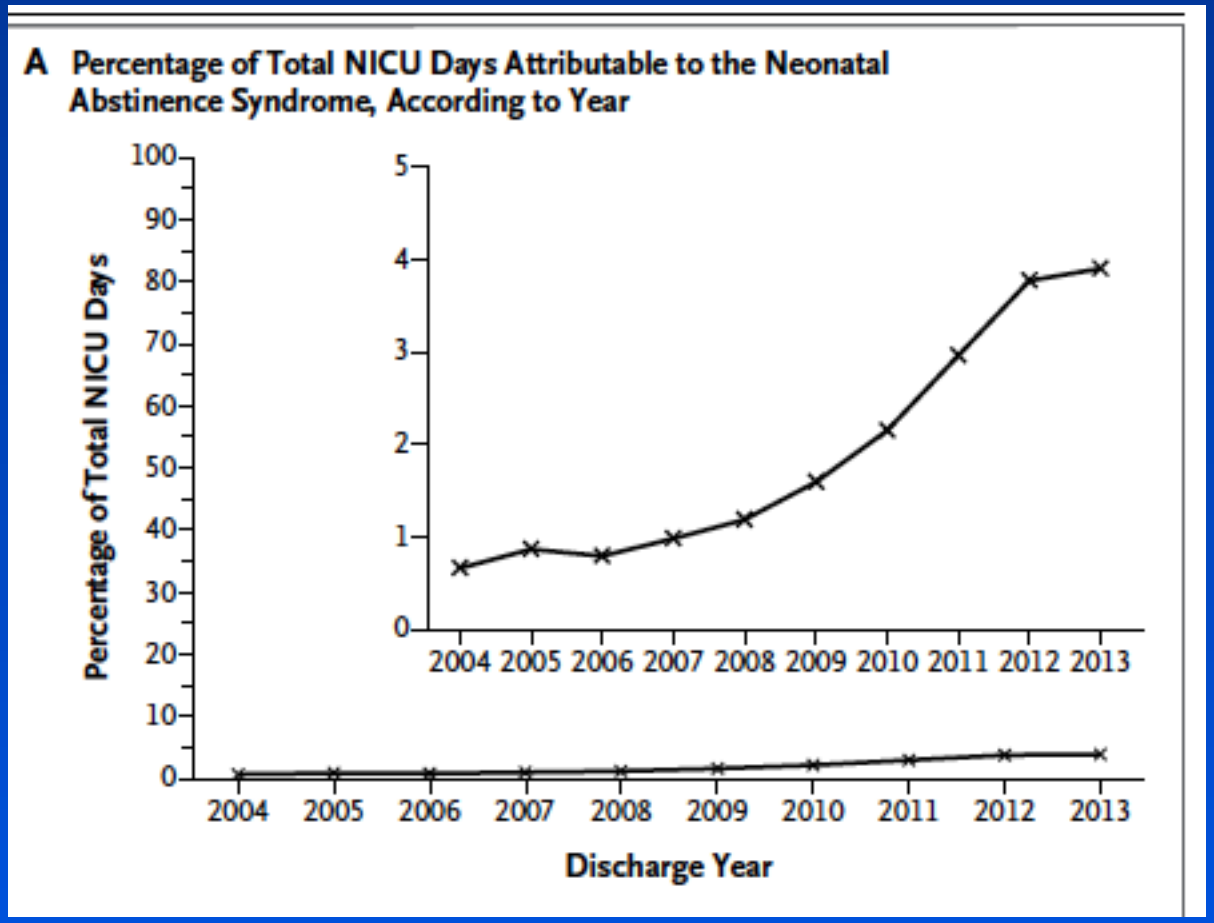


Figure 1. Annualized NICU Admission Rates for the Neonatal Abstinence Syndrome and Median Length of Stay, According to Year.

I bars in Panel B represent interquartile ranges. NICU denotes neonatal intensive care unit.

Tolia, et al
NEJM 2015



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Primary and Secondary Outcomes in the Methadone and Buprenorphine Groups

Table 2. Primary and Secondary Outcomes in the Methadone and Buprenorphine Groups.*

Outcome	Methadone (N=73)	Buprenorphine (N=58)	Odds Ratio (95% CI)	P Value
Primary outcomes				
Treated for NAS — no. (%)	41 (57)	27 (47)	0.7 (0.2–1.8)	0.26
NAS peak score	12.8±0.6	11.0±0.6		0.04
Total amount of morphine for NAS — mg	10.4±2.6	1.1±0.7		<0.0091†
Duration of infant's hospital stay — days	17.5±1.5	10.0±1.2		<0.0091†
Infant's head circumference — cm	33.0±0.3	33.8±0.3		0.03
Secondary neonatal outcomes				
Duration of treatment for NAS — days	9.9±1.6	4.1±1.0		<0.003125†
Weight at birth — g	2878.5±66.3	3093.7±72.6		0.03
Length at birth — cm	47.8±0.5	49.8±0.5		0.005
Preterm, <37 wk — no. (%)	14 (19)	4 (7)	0.3 (0.1–2.0)	0.07
Gestational age at delivery — wk	37.9±0.3	39.1±0.3		0.007
Apgar score				
1 min	8.0±0.2	8.1±0.2		0.87
5 min	9.0±0.1	9.0±0.1		0.69
Secondary maternal outcomes				
Cesarean section — no. (%)	27 (37)	17 (29)	0.6 (0.2–2.0)	0.23
Maternal weight gain — kg	8.6±1.0	8.3±0.9		0.80
Abnormal fetal presentation during delivery — no. (%)	10 (14)	3 (5)	0.3 (0.0–2.4)	0.09
Analgesia during delivery — no. (%)	60 (82)	49 (85)	1.1 (0.3–4.8)	0.85
Positive drug screen at delivery — no. (%)	11 (15)	5 (9)	0.5 (0.1–2.7)	0.27
Medical complications at delivery — no. (%)	37 (51)	18 (31)	0.5 (0.2–0.9)	0.03
Did not complete study — no. (%)	16 (18)	28 (33)	2.6 (1.3–5.6)	0.02
Amount of voucher money earned for drug-negative tests — U.S. $	1,570.00±121.72	1,391.39±123.59		0.31
No. of prenatal obstetrical visits	8.8±0.5	8.7±0.4		0.86

* Plus–minus values are means ±SE. In accordance with the alpha level chosen for the tests of significance, 99.09% confidence intervals (CIs) were used for the primary outcome measures, and 99.6825% CIs were used for the neonatal and maternal secondary outcome measures. The number of patients who underwent randomization was 175, the number who did not complete the study was 44, and the number who did complete the study was 131. A small percentage of data was missing. For four of the five primary outcomes, the number of patients with missing data was 1 in each medication group except for the outcome on length of hospital stay for neonates, for which no data were missing. For two of the seven secondary neonatal outcomes, the number of patients with missing data was 1 in each medication group for days treated for NAS and 1 in the methadone group for infant length at birth. For four of the nine secondary maternal outcomes, the number of patients with missing data in the methadone group was 2 for maternal weight gain, 2 for abnormal fetal presentation during delivery, 1 for positive drug screen at delivery, and 3 for amount of voucher money earned; the number of patients with missing data in the buprenorphine group was 4 for maternal weight gain, 1 for positive drug screen at delivery, and 1 for voucher money earned.

† These P values were calculated in accordance with prespecified thresholds for significance.

Jones HE et al. N Engl J Med 2010;363:2320-2331

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Summary

- Addiction is a common problem, across all sectors of society.
- It is frequently undiagnosed or, if recognized ignored.
- Opioid addiction is on the rise.
  - Appropriate therapies are available, but may be difficult to access.
  - Agonist therapy is the preferred modality for patients with long-standing opioid addiction.