

Evidenced Based Treatment for Opioid Addiction



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Drug Dependence: A Chronic Medical Illness

- Genetic Heritability – twin studies
 - ✓ Hypertension – 25-50%
 - ✓ Diabetes – Type 1: 30-55%; Type 2: 80%
 - ✓ Asthma – 36-70%
 - ✓ Nicotine – 61% (both sexes)
 - ✓ Alcohol – 55% (males)
 - ✓ Marijuana – 52% (females)
 - ✓ Heroin – 34% (males)
- Voluntary Choice – shaped by personality and environment
- Pathophysiology – neurochemical adaptations
- Treatment Response
 - ✓ Medications – effectiveness and compliance
 - ✓ Behavioral interventions



Radio personality Rush Limbaugh for

OxyContin[®]

"OxyContin[®] helped me deal with the pain of living in a world that just didn't resemble my perceptions or my claims."



WARNING: This drug has been shown to cause sudden distress in long-time abusers.



DEATH AMONG THE POPPIES



American newspapers tirelessly editorialized against the perceived threats of opium.



The Yellow Peril soon became a familiar threat.



Opioids

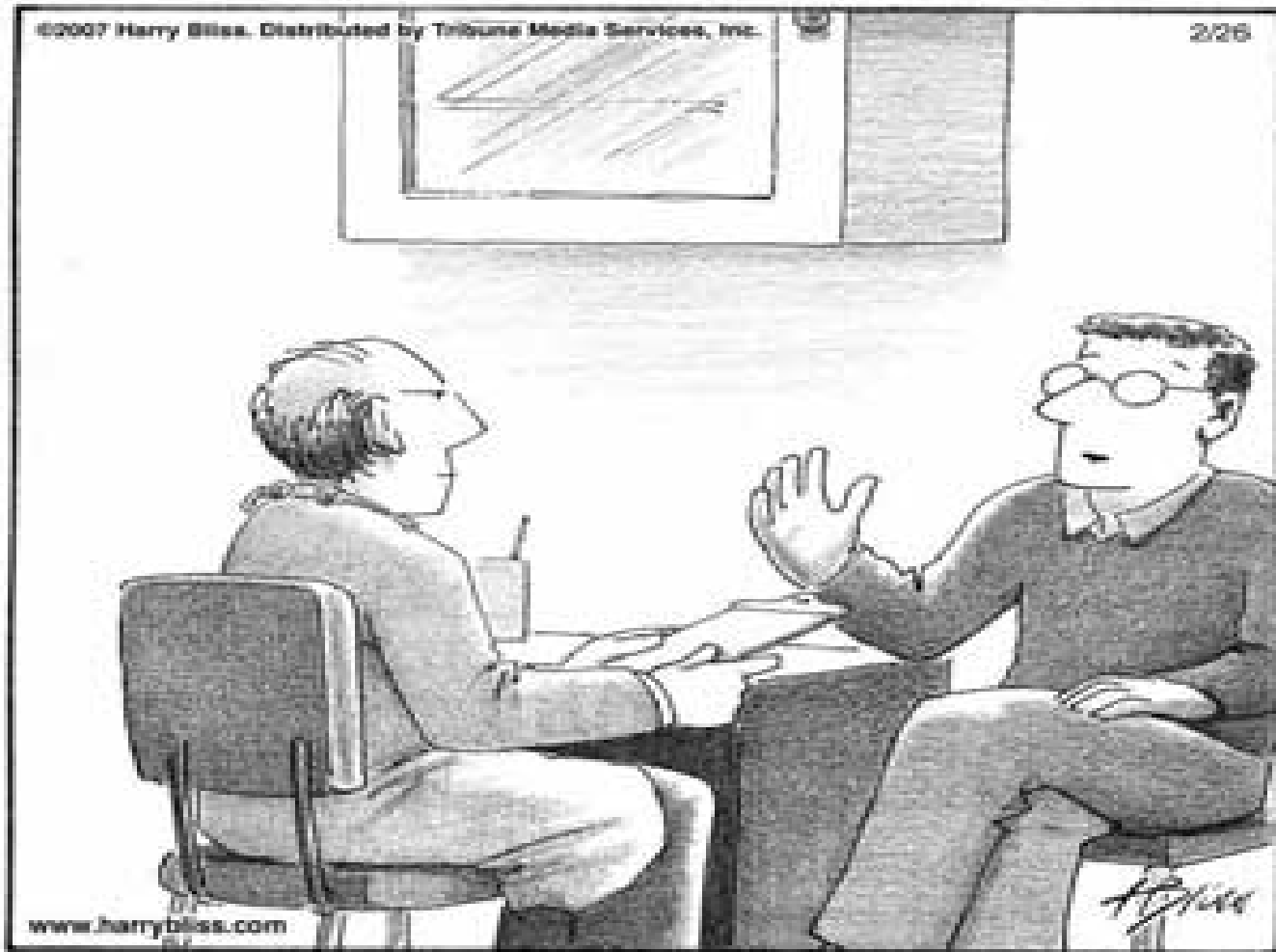


- Dates to 4,000 BC
- Mimics endorphin activity
- Natural - Opium, morphine, codeine
- Semi-synthetic- Heroin, Dilaudid, Vicodin
- Synthetics - Darvon, Demerol, Fentanyl, Oxycontin® (oxycodone), methadone

Prescription Opioids



- OxyContin® – an oral, controlled release form of the drug oxycodone – crush the tablet = heroin-like high
- Percodan®, Percocet® – oxycodone
- Darvon® – propoxyphene
- Vicodin®, Lortab® – hydrocodone
- Dilaudid® – hydromorphone
- Duragesic® – fentanyl



"What's the difference between being addicted to painkillers and just really, really liking them a lot?"

OPIOIDS

ACUTE USE SYMPTOMS



- **DECREASED HEART RATE, BLOOD PRESSURE AND RESPIRATION RATE**
- **CONSTRICTED PUPILS**
- **DROOPING EYELIDS AND SLURRED SPEECH**
- **SLEEPINESS / SEDATION**
- **NAUSEA**
- **RELIEF OF PHYSICAL / EMOTIONAL PAIN
(ANALGESIA)**

OPIOIDS

CHRONIC USE SYMPTOMS



- CONSTIPATION
- DECREASED SEXUAL INTEREST
- TOLERANCE

ILLICIT OPIOIDS

- CRIMINAL LIFESTYLE TO SUPPORT HABIT
- LIFESTYLE CHANGES
- HEPATITIS AND HIV INFECTION THROUGH NEEDLE SHARING AND OTHER HIV HIGH RISK ACTS

OPIOIDS

WITHDRAWAL SYMPTOMS




- FLU-LIKE SYMPTOMS
 - ✓ RUNNY NOSE
 - ✓ WATERY EYES
 - ✓ DILATED PUPILS
 - ✓ "GOOSE FLESH"
 - ✓ STOMACH CRAMPS & DIARRHEA
 - ✓ INCREASED HEART RATE & BLOOD PRESSURE
 - ✓ INTENSE DISCOMFORT

4-7 days (short-acting opioids)

10-21 days (methadone, if on long term)

NIH Consensus Panel on Effective Medical Treatment of Opiate Addiction



- 12 member multi-disciplinary panel, Nov. 1997
- heard testimony from 25 experts
- reviewed 941 research reports published over the period Jan. 1994 - Sept. 1997

“Of the various treatments available, MMT, combined with attention to medical, psychiatric, and socioeconomic issues, as well as drug counseling, has the highest probability of being effective.”

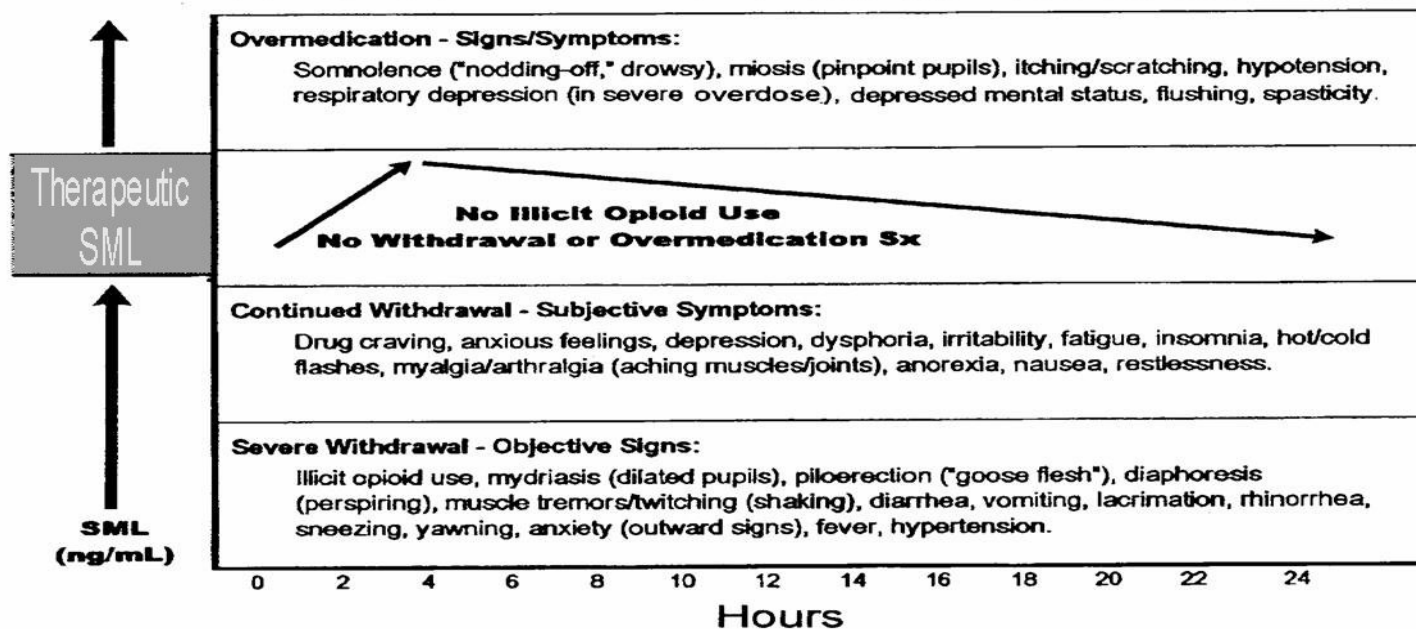
Comparing Two Opioid Agonists: Methadone and Heroin



Methadone	Heroin
Orally effective. No risk of infection.	Not orally effective. Injection use is a risk factor for transmission of infectious diseases.
Long acting. Administered once a day.	Short acting. Must be administered several times a day.
Causes no sedation or euphoria.	Can cause significant sedation and/or euphoria.

Methadone Dose: How much is enough?

Table 1
Signs/Symptoms of Opioid Withdrawal (Abstinence Syndrome) and Overmedication (2, 3, 9-12)



SML+ serum methadone level

As the serum methadone level rises, the objective signs of abstinence syndrome disappear and the clinician uses subjective symptoms as a guide for further dose increases. At the optimal methadone dose, the serum methadone level stays in the therapeutic range throughout the 24 hour period. If the methadone dose is too high, signs/symptoms of overmedication appear

Opiate Substitution Treatment Goals



● **Primary Goals:**

- ✓ Reduction in of illicit opiate use and licit opiate misuse.
- ✓ Retention in treatment for 1-2 years or more.

● **Secondary Goals:**

- ✓ Reduction in cocaine, alcohol, and other drug abuse.
- ✓ Reduction in transmission of infectious diseases by unsterile injection equipment.
- ✓ Reduction in criminal activity.
- ✓ Increase in pro-social activity — employment, education, child care, etc.

Treatment Requirements



- Attendance for observed dosing 6 days a week for the first 90 days
- Take-home doses permitted after 90 days but only to those patients meeting a number of criteria
- At least once per month urinalysis
 - ✓ Some clinics observe collection; some don't
 - ✓ Some clinics have contingencies (+ & -); some don't
 - ✓ Some agencies administer alcohol breath tests; some don't
- Assessment and counseling
- Additional education, i.e., HIV/HCV, family planning

Approaches to Providing Comprehensive Care and Maximizing Patient Retention

TIP 43, Chapter 8

- Individualized treatment planning & delivery; phases of treatment (Ch. 6 & 7)
- Counseling case management services
- Psychiatric services
- Medical screening and coordination of care delivery
 - ✓ HIV/HCV education and risk reduction interventions
- Contingency Management
- Motivational Interviewing
- Relapse prevention

Weaving Evidenced-Based Practices into Medication-Assisted Treatment for Opioid Dependence



- Individualized treatment
 - ✓ Use the Addiction Severity Index (ASI) at intake to identify patient strengths and unmet needs
 - ✓ Use ASI to guide treatment planning and delivery
 - Use aggregate ASI data for program planning
 - Use follow-up ASI data for program evaluation
- Motivational Interviewing
 - ✓ Train staff in its application
 - ✓ Supervise staff in its utilization

Weaving Evidenced-Based Practices into Medication-Assisted Treatment for Opioid Dependence



- Motivational incentives
 - ✓ Reward drug-free urine samples with additional take-home privileges and vouchers
 - Pierce, JM, et. al., *Effects of Lower-Cost Incentives on Stimulant Abstinence in Methadone Maintenance Treatment*, *Ach. Gen. Psychiatry*. 2006;63:201-208.
 - ✓ Reward counseling attendance with vouchers
- Use of additional addiction treatment medications
 - ✓ disulfiram for alcohol and/or cocaine addiction
 - ✓ nicotine replacement

Methadone & Pregnancy

- Fetal outcomes better on MMT than heroin
- Detoxification from opiates risky for fetus
- Methadone dose adjustments during pregnancy
 - ✓ May need “split” dosing to improve serum stability
- Attention to prenatal care during pregnancy
- Some infants have abstinence syndrome within 72 hrs. of birth; may require pharmacotherapy
 - ✓ NAS may be associated with mothers’ level of smoking during pregnancy (Choo, et.al., 2004)
- Breastfeeding OK with MMT unless otherwise contraindicated, e.g., blood-borne infections

For further information see TIP 43, Chapter 13

Methadone Maintenance vs. 180 Day Detoxification

12 month study of 179 opioid dependent patients randomly assigned to:

- **Methadone Maintenance**

- ✓ mean dose=85.3mg

- ✓ for 14 months

- **180 Day Methadone Detoxification**

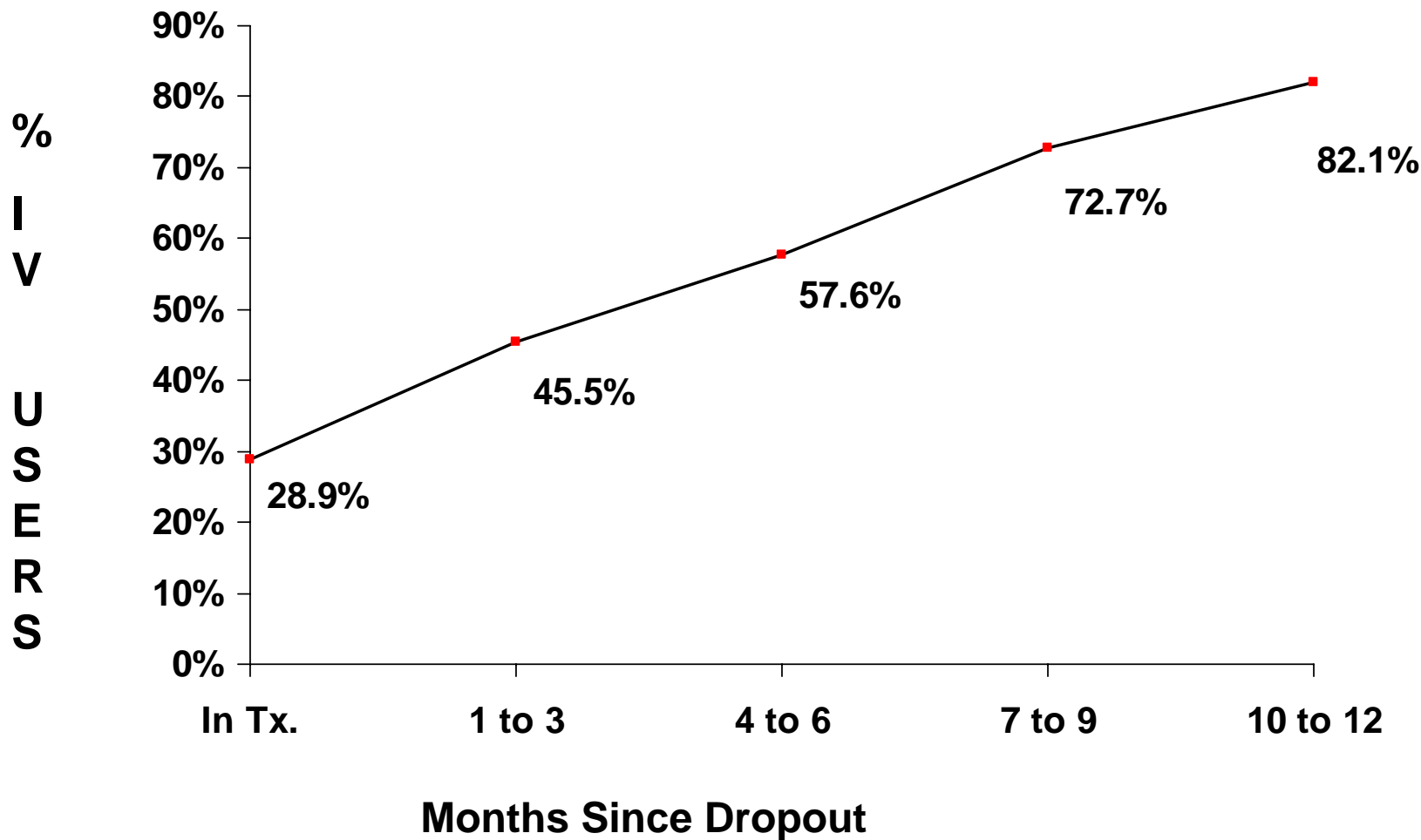
- ✓ mean dose=86.3 mg prior to taper at 120 days

- ✓ followed by psychosocial Tx for 8 months

➤ **“Methadone maintenance therapy resulted in greater treatment retention and lower heroin use rates than did detoxification.”**

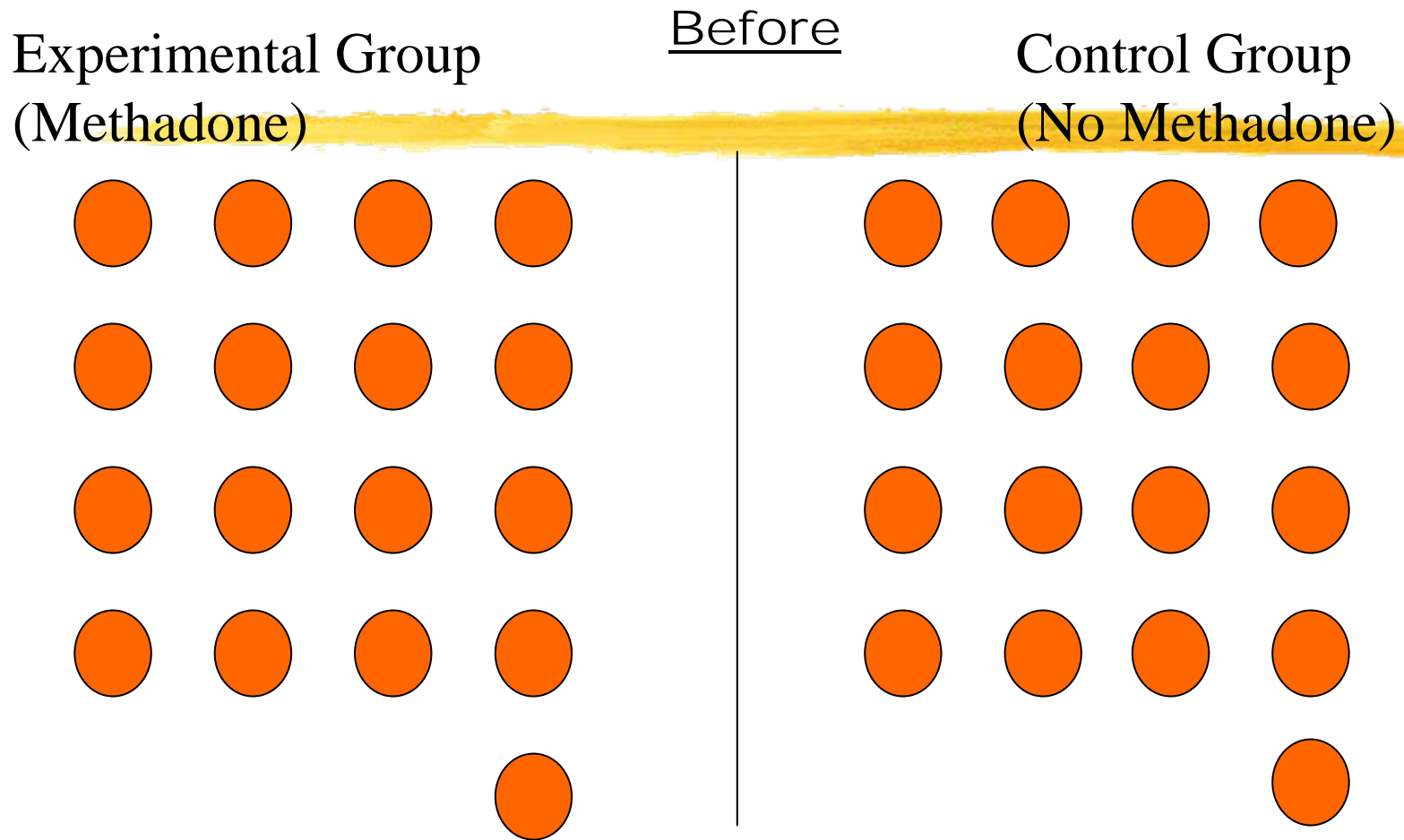
K.L. Sees et al., JAMA 2000

Return to I.V. Drug Use Following Premature Termination of Treatment



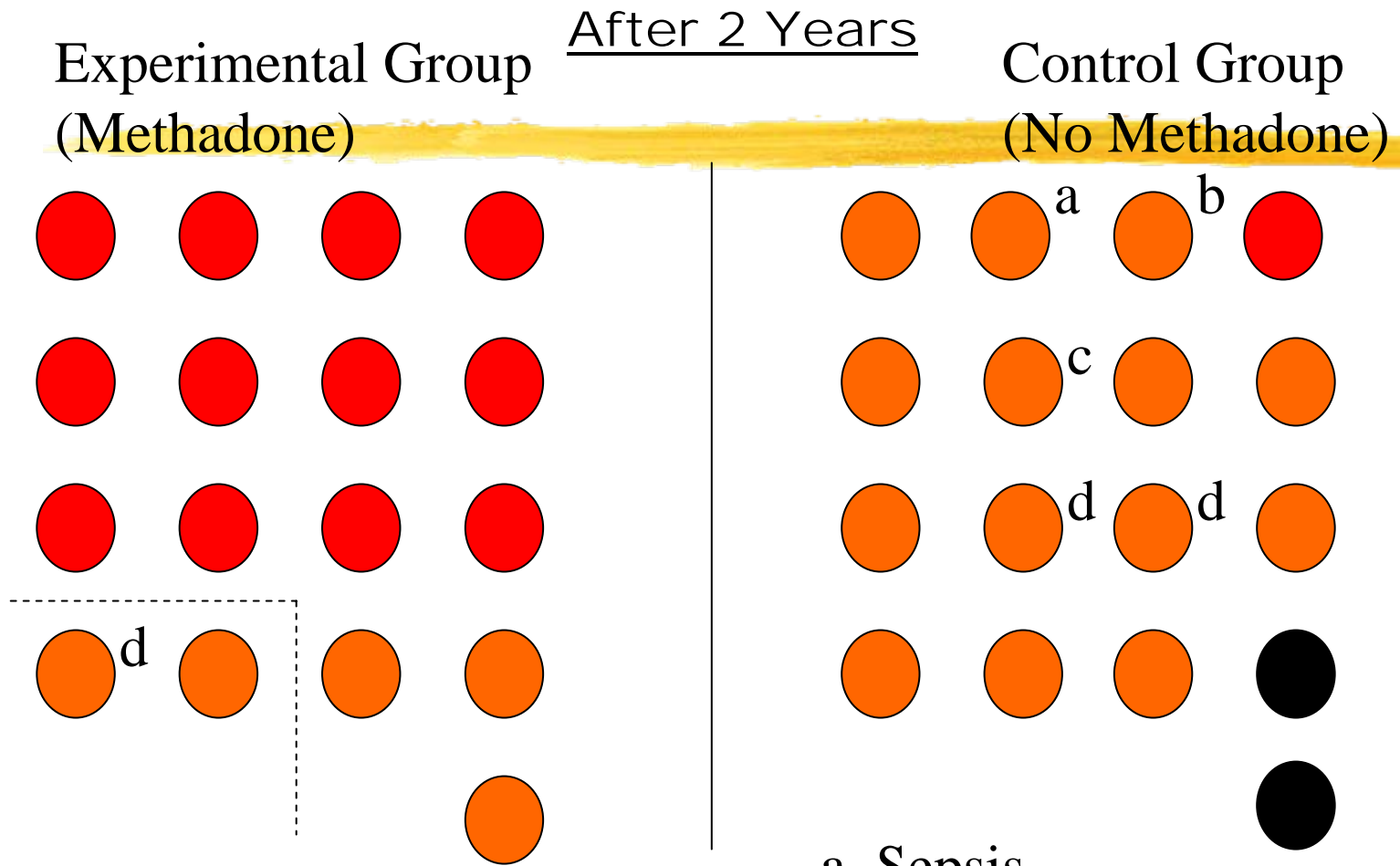
Adapted from: Ball & Ross, 1991.

Swedish Methadone Study



Gunne & Gronbladh, 1981

Swedish Methadone Study



- a Sepsis
- b Sepsis and Endocarditis
- c Leg Amputation
- d In Prison

Death Before, During, and After Opioid Maintenance Treatment



Clausen T., et al. *Drug Alcohol Dependence*
2008; 94(1-3):151-157.

Summary by Jeffrey A. Samet, MD, MA, MPH

www.aodhealth.org

Objectives/Methods



- This Norwegian study sought to determine the extent to which opioid maintenance therapy (OMT) reduced mortality in patients with opioid dependence.
- Researchers linked data from a national death registry to a national database of people either on a waiting list for OMT, receiving OMT (predominantly methadone), or who had discontinued OMT.
- In the 3789 patients identified, risk of death during treatment was compared with risk before and after treatment.

Results



- Over 7 years, 213 patients died.
- 79% of deaths in the waiting-list group, 27% of deaths in the treatment group, and 61% of deaths in the discontinued-treatment group were attributed to overdose.
- Mortality risk was significantly lower in patients receiving treatment than in patients on the waiting list (relative risk [RR], 0.5; death rates of 1.4 versus 2.4 per 100 person years, respectively).
- Risk was highest among men who discontinued treatment (RR, 1.8 compared with men on the waiting list).

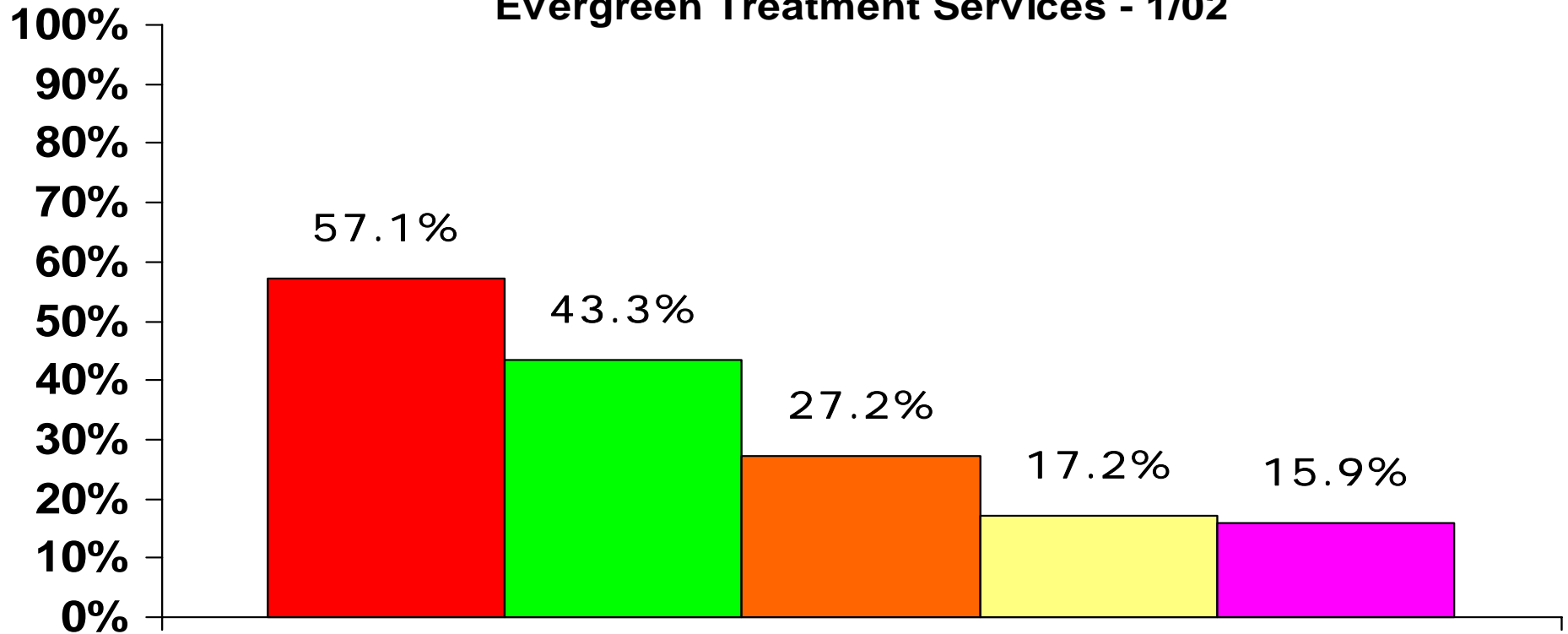
Comments



- This rigorous investigation provides further strong evidence that OMT lowers mortality risk in opioid-dependent patients.
- Increasing cases of overdose death attributed to physician-prescribed methadone for pain have increased the potential for negative public backlash against methadone.
- Therefore, these results may play an important role in policy efforts supporting the continued use of OMT to treat patients with opioid dependence.

Drug Use & Length of Time in Methadone Treatment

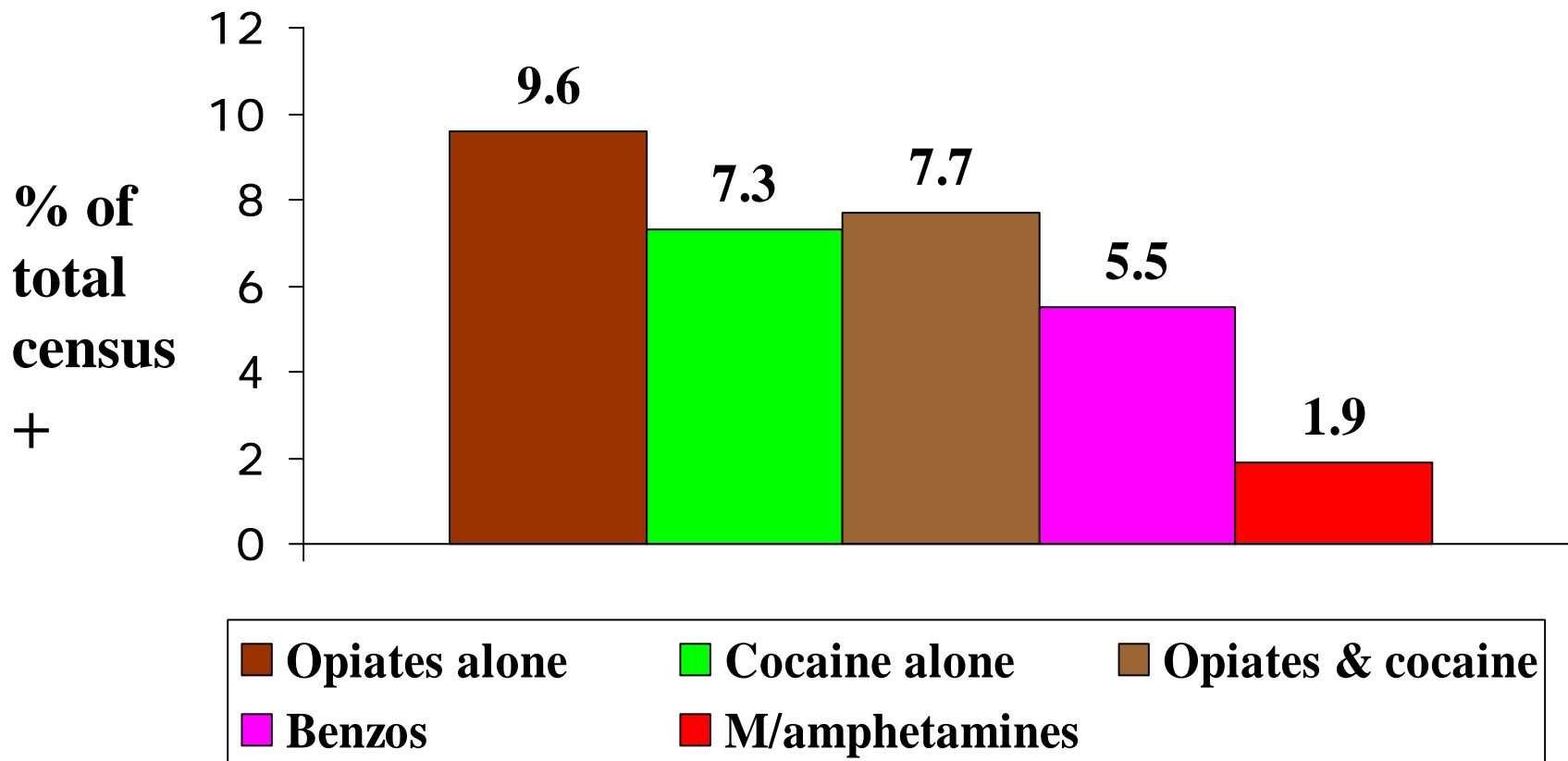
Evergreen Treatment Services - 1/02



% of Time Cohort with a positive U.A. during month

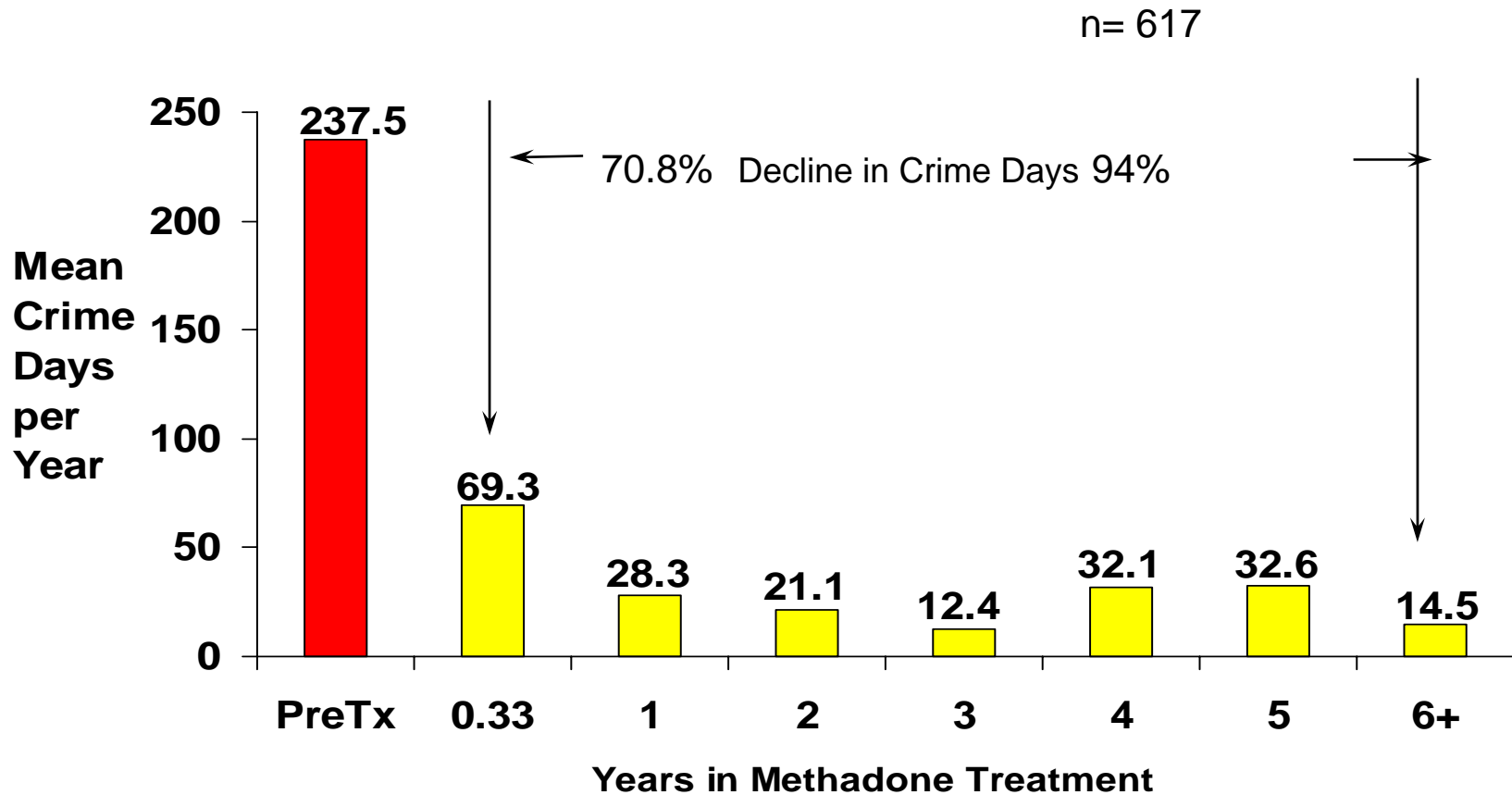
■ < 90 days ■ 91 - 180 days ■ 181 days - 1 year ■ 1 - 2 years ■ > 2 years

Drug Use by Patients in Methadone Treatment



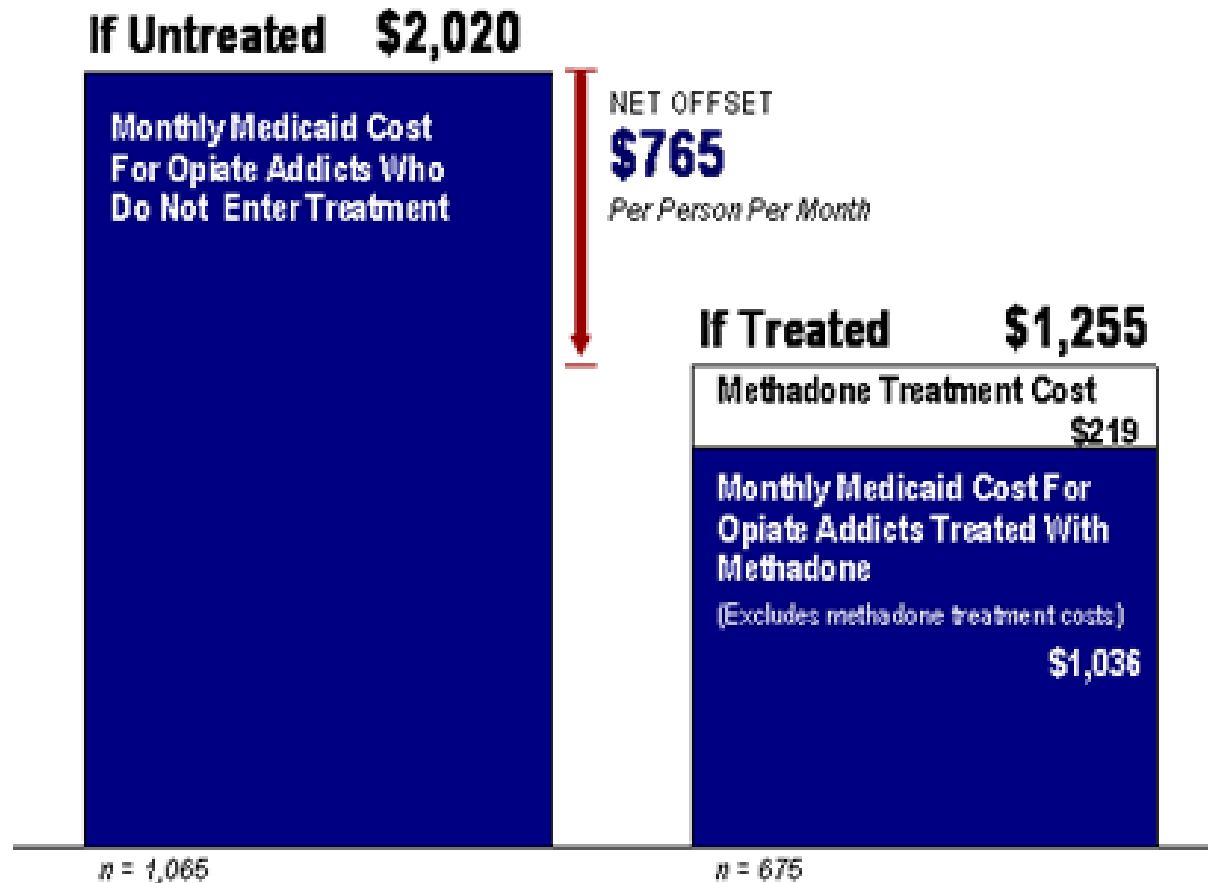
Evergreen Treatment Services, May 2003 n = 781

The Effects of Methadone Treatment on Crime Days



Adapted from: Ball & Ross, 1991.

Methadone Treatment For Opiate Addiction Lowers Health Care Costs



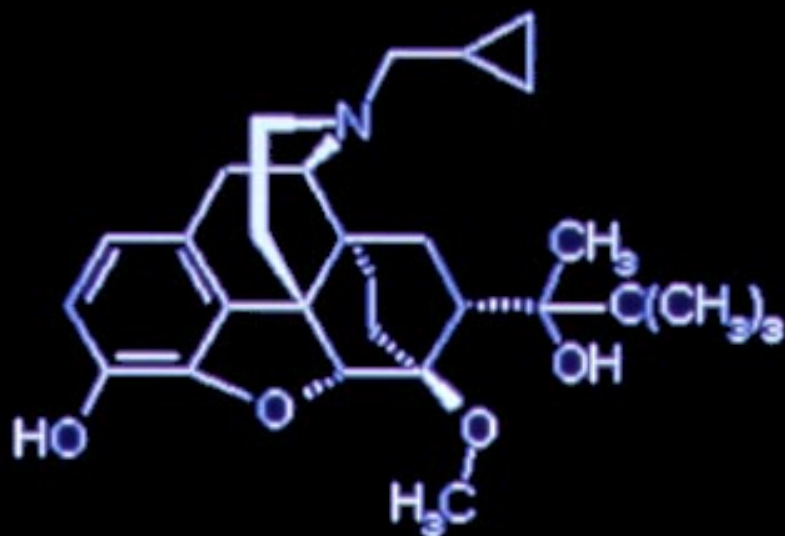
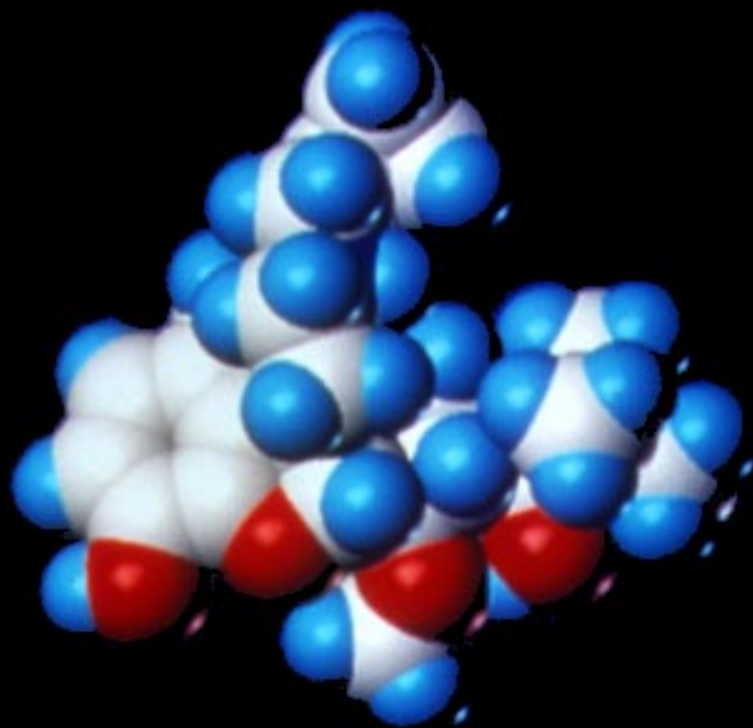
Source: State of Washington, DSHS, Research & Data Analysis Division, Report 4.49fs, June, 2004

Characteristics of Successful Methadone Treatment Programs



- ✓ **Adequate Dosing Policies**
 - ✧ Average Dose Between 60 & 120mg.
- ✓ **Comprehensive Services**
- ✓ **Well-trained & Stable Staff**
- ✓ **Individualized Treatment**
- ✓ **Coordinated Services**
 - ✧ Medical, Counseling & Administration

BUPRENORPHINE



Overview of Buprenorphine



- ✓ Buprenorphine, a thebaine derivative (classified in the law as a narcotic – Schedule III)
- ✓ High potency
- ✓ Produces sufficient agonist effects to be detected by the patient
- ✓ Long duration of action when used for the treatment of opioid dependence contrasts with its relatively short analgesic effects


Function at Receptors: Partial Agonists

**Mu
receptor**

Partial agonist binding ...

- ①** activates the receptor at lower levels
- ②** is relatively less reinforcing
- ③** is a less abused opioid type
- ④** includes buprenorphine

Buprenorphine Therapeutic Niche



- Unmet need for a medication between:
 - ✓ methadone (full agonist) and
 - ✓ naltrexone (competitive antagonist)
- Partial agonist fits the unmet need

Properties of a Partial μ -Opiate Agonist



- Ceiling effect on respiratory depression
- Less physical dependence capacity
- Blocks withdrawal in mildly dependent people
- Precipitates withdrawal in moderate to severely dependent people

Properties Attributed to Slow Dissociation Effect at μ -Opiate Receptors

- Reduces expression of opioid withdrawal syndrome
- Has only mild subjective effects
- Blocks effect of injected agonists—hard to dislodge

Combination of Buprenorphine Plus Naloxone

- Sublingual buprenorphine has good bioavailability
- Addition of naloxone to buprenorphine to decrease abuse potential of tablets
- Combination ratio is 4 to 1 (buprenorphine to naloxone)
- Buprenorphine tablet with naloxone marketed as Suboxone®
- Buprenorphine tablet without naloxone marketed as Subutex ®

Addition of Naloxone Reduces Abuse Potential



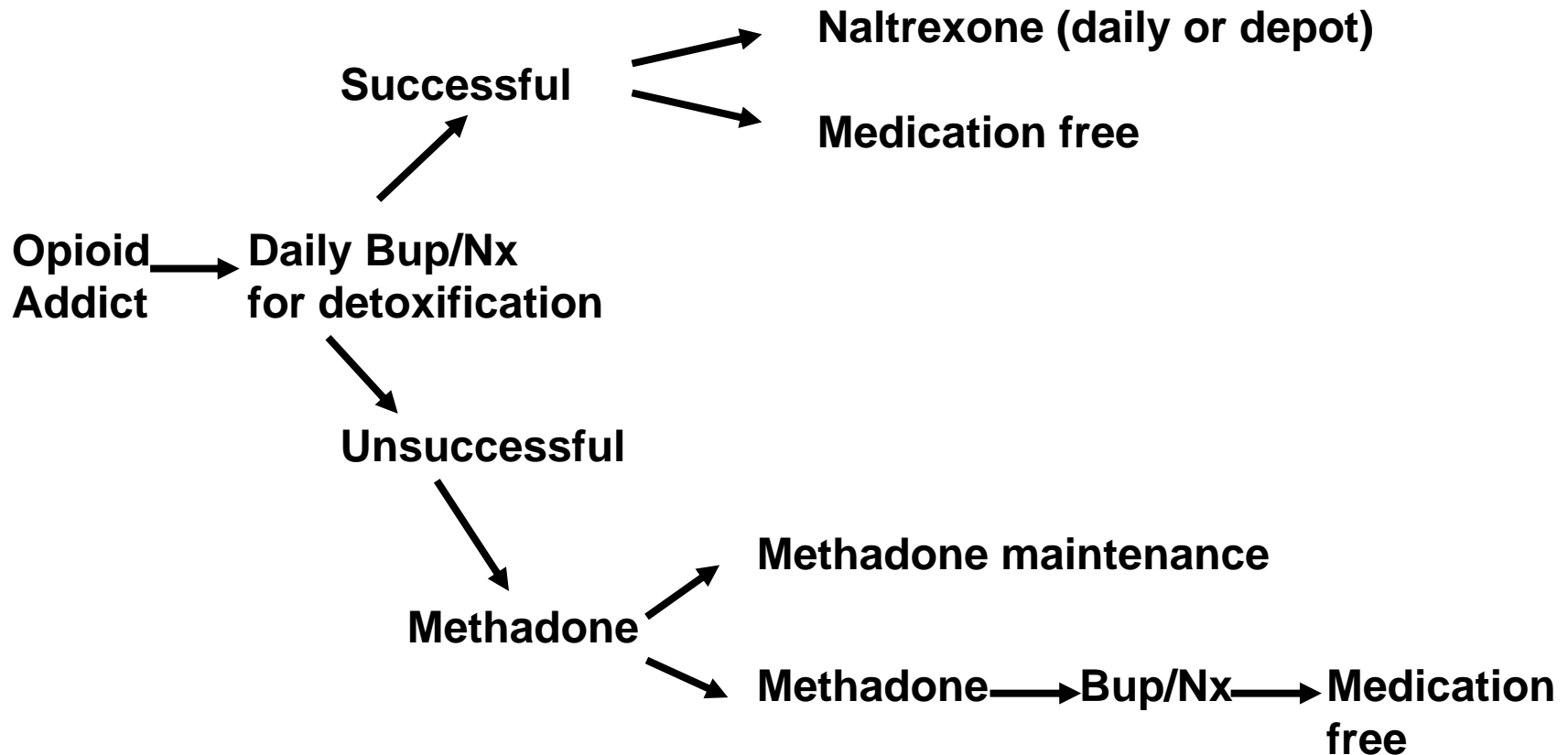
- Naloxone will block buprenorphine's effects by the IV but not the sublingual route
- Sublingual absorption of buprenorphine @ 70%; naloxone @ 10%
- If injected, BUP/NX will precipitate withdrawal in a person moderately to severely dependent

Clinic vs. Office-Based Treatment



- Methadone:
 - ✓ available for addiction treatment only in approved clinics (OTPs)
 - ✓ Regulation-driven – Clinics must provide array of counseling, drug testing and dispensing services
- Buprenorphine:
 - ✓ Available mostly through physicians in office-based practice; limited availability in OTPs
 - ✓ Guideline-driven – Physicians not required to provide any additional services

Agonist Pharmacotherapy Options for Opioid Dependence



Opiate Antagonists



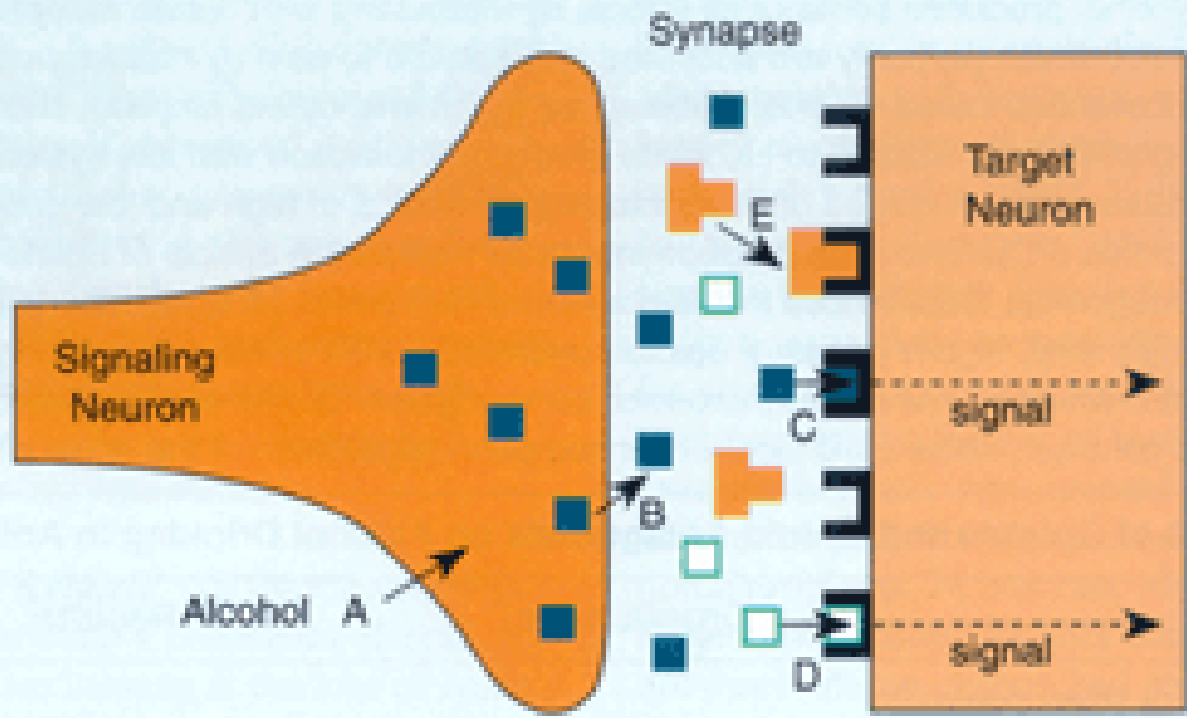
- **Naloxone** (NARCAN®)

- ✓ treatment for acute opiate overdose

- **Naltrexone** (ReVia® Vivitrex®)

- ✓ detoxification from physical dependence on opiates
 - ✓ opiate “blocker” - aid to maintenance of abstinence from opiates
-

➤ **Clonidine** (Catapres®) - not an antagonist - suppresses withdrawal symptoms



T = Naltrexone ■ = Endogenous Opioids
J = Receptor □ = Exogenous Opiates

Resources

- TIP 43, *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs* – www.health.org
- TIP 40, *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* – www.health.org
- Addiction Treatment Forum: www.atforum.com
- Web sites:
 - ✓ kap.samhsa.gov – CSAT's Knowledge Application Program
 - ✓ www.aatod.org – AATOD
 - ✓ buprenorphine.samhsa.gov/index.html – CSAT's buprenorphine Web site, including FAQs
 - ✓ www.drugpolicy.org – Drug Policy Alliance
 - ✓ About Methadone
 - ✓ www.nida.nih.gov – NIDA



Resources

- www.nida.nih.gov – NIDA
Addiction Science & Clinical Practice

