

# Opioids

## Research to Practice

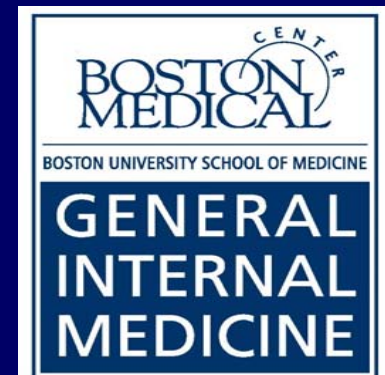
CRIT Program

May 2011

Daniel P. Alford, MD, MPH  
Associate Professor of Medicine  
Boston University School of Medicine  
Boston Medical Center



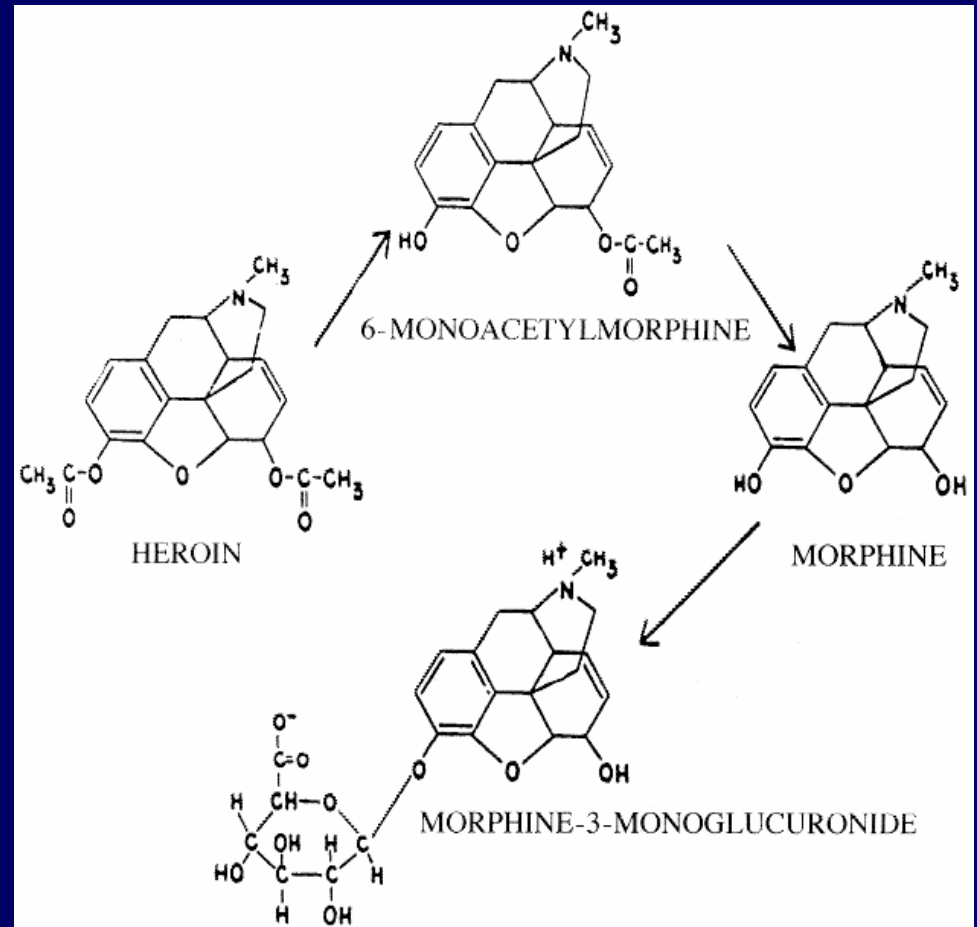
**Boston University** School of Medicine



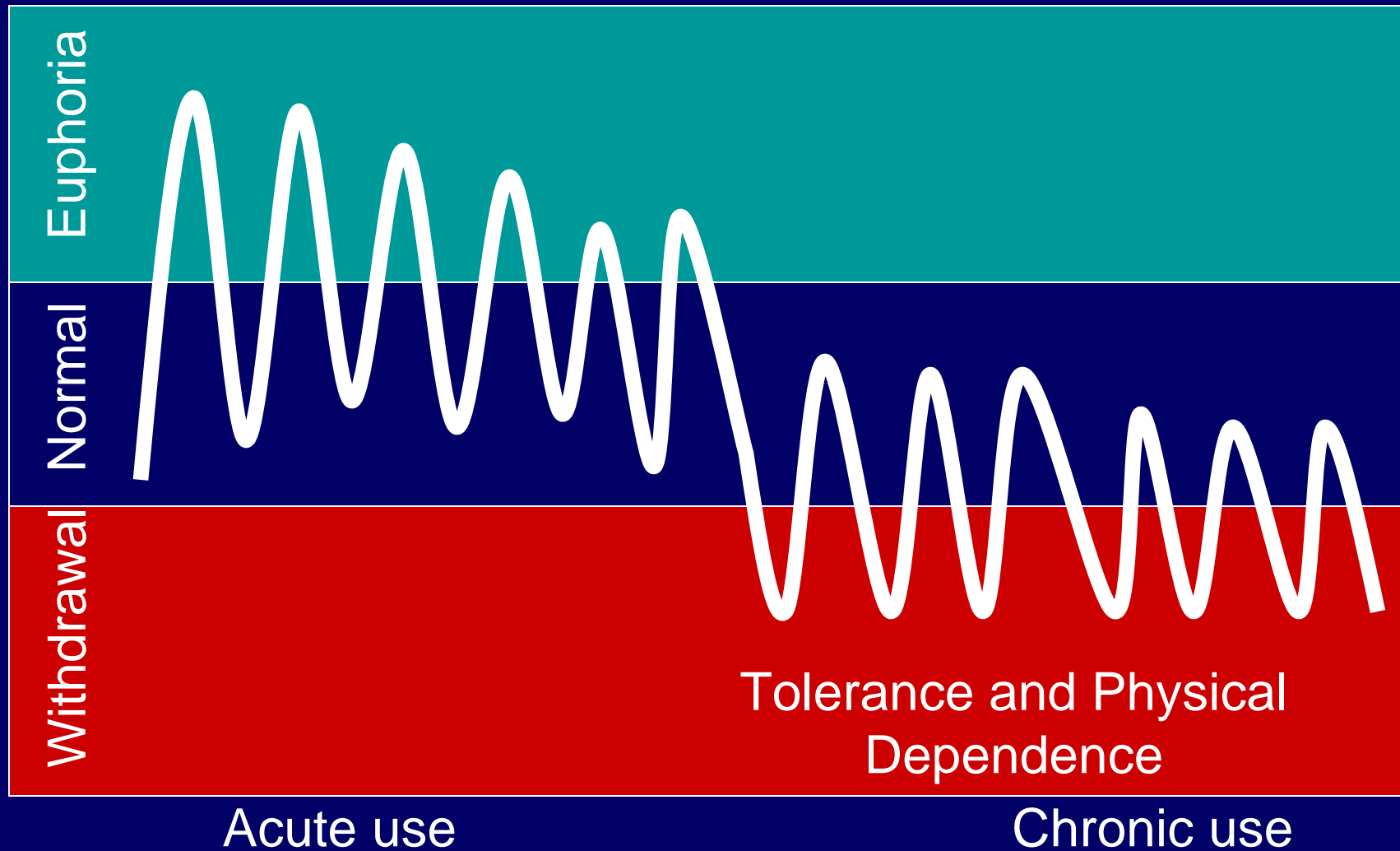
- 32 yo female brought in after “heroin overdose”
- Brisk response to IV naloxone 0.4 mg
- Re-sedation after 1 hr requiring repeat naloxone
- Arm cellulitis at injection drug use site
- Admitted for “drug overdose”, “persistent altered mental status” and “arm cellulitis”

# Why is heroin so pleasurable ?

- Heroin is highly lipid soluble
- Crosses blood brain barrier within 15 seconds="rush"
- After IV administration 68% heroin in brain compared to <5% of morphine
- Within 30 minutes metabolized to morphine
- **HEROIN** is a prodrug of **MORPHINE**



# Natural History of Opioid Dependence



# Overdose Epidemiology

- Injection heroin users, annual mortality rate 2%
  - 6-20 X that of non-drug using peers
- Half attributable to overdose
  - Late 20s to early 30s
  - Use for 5-10 years, only 17% novice users
  - Multiple drug use (70%)
- High risk periods
  - First 12 months after addiction treatment and
  - First 2 weeks after release from incarceration

## Substance abuse history

- ½ gram of heroin/day
- Intranasal use for 6 months then IV for 7 years
- Had been clean for 2 years by going to NA meetings but relapsed 3 months ago
- Denies sharing needles
- History of 10 detox's, no maintenance treatment
- No other drug, alcohol or tobacco use
- HIV and hepatitis C negative in the past
- Unemployed elementary school teacher
- Lives with husband (in recovery) and 2 young children
- Now complaining of opioid withdrawal
  - How will you assess and treat her?

# Opioid Withdrawal Assessment

Hours after use	Grade	Symptoms / Signs
4-6	0	Anxiety, Drug Craving
	1	Yawning, Sweating, Runny nose, Tearing eyes, Restlessness Insomnia
6-8	2	Dilated pupils, Gooseflesh, Muscle twitching & shaking, Muscle & Joint aches, Loss of appetite
8-12	3	Nausea, extreme restlessness, elevated blood pressure, Heart rate > 100, Fever
12-72	4	Vomiting / dehydration, Diarrhea, Abdominal cramps, Curled-up body position

**Clinical Opiate Withdrawal Scale (COWS):** *pulse, sweating, restlessness & anxiety, pupil size, aches, runny nose & tearing, GI sx, tremor, yawning, gooseflesh (score 5-12 mild, 13-24 mod, 25-36 mod sev, 36-48 severe)*

# Questions...

- **Who sees acute opioid withdrawal on the inpatient service?**
- **Of those that do, who uses methadone to treat withdrawal on the inpatient service?**



# Inpatient Short-term Goals

- Prevent/treat acute opioid withdrawal
  - Inadequate treatment may prevent full treatment of medical/surgical condition
- Do not expect to cure opioid dependence during this hospital stay
  - Withholding opioids will not cure patient's addiction
  - Giving opioids will not worsen patient's addiction
- Diagnose and treat medical illness
- Initiate substance abuse treatment referral

# Inpatient Short-term Goals

- Methadone is the best choice!  
*or buprenorphine (more expensive)*
- Other
  - Clonidine (hyperadrenergic state)
  - + NSAIDS (muscle cramps and pain)
  - + Benzodiazepines (insomnia)
  - + Dicyclomine (abdominal cramps)
  - + Bismuth subsalicylate (diarrhea)

# Methadone Hydrochloride

- Full opioid agonist available in tablets, oral solution, parenteral
- PO onset of action 30-60 minutes
- Duration of action
  - 24-36 hours to treat opioid addiction
  - 6-8 hours to treat pain
- Proper dosing for opioid addiction
  - 20-40 mg for acute withdrawal
  - > 80 mg for craving, “narcotic blockade”

# Inpatient Methadone Dosing Guidelines

- Assess signs and symptoms of acute opioid withdrawal
- Reassure patient
- Discuss specific dose and goals openly with patient and nursing staff
- Don't use heroin : methadone conversions

# Inpatient Methadone Dosing Guidelines

- Start with 20 mg of methadone
- Reassess q 2-3 hours, give additional 5-10 mg until withdrawal signs abate
- Do not exceed 40 mg in 24 hours
- Monitor for CNS and respiratory depression

# Inpatient Methadone Dosing Guidelines

- On following day, give total dose QD
- Goal is to alleviate acute withdrawal
- Patient will continue to crave heroin
- Discuss taper vs maintained dose w/ pt daily
- Referral for long-term substance abuse treatment

# Inpatient Methadone Dosing Guidelines

- Maintained dose option
  - Give same dose each daily including day of discharge
  - Allows 24-36 hour withdrawal-free period after d/c
- Tapered dose option
  - If patient requests a taper, decrease by 5 mg per day and stop taper if patient requests it
  - Don't prolong hospitalization to complete taper
- Don't give a prescription for methadone

## *Hospital course*

- Arm Cellulitis treated with IV Vancomycin
- Opioid withdrawal
  - Day 1 Methadone 20 mg
  - Day 2
    - Very anxious, demanded increase in dose
    - Was off the floor for 2 hours
    - Repeat urine drug test was positive for “**opiates**”

**How do you interpret this drug test result?**

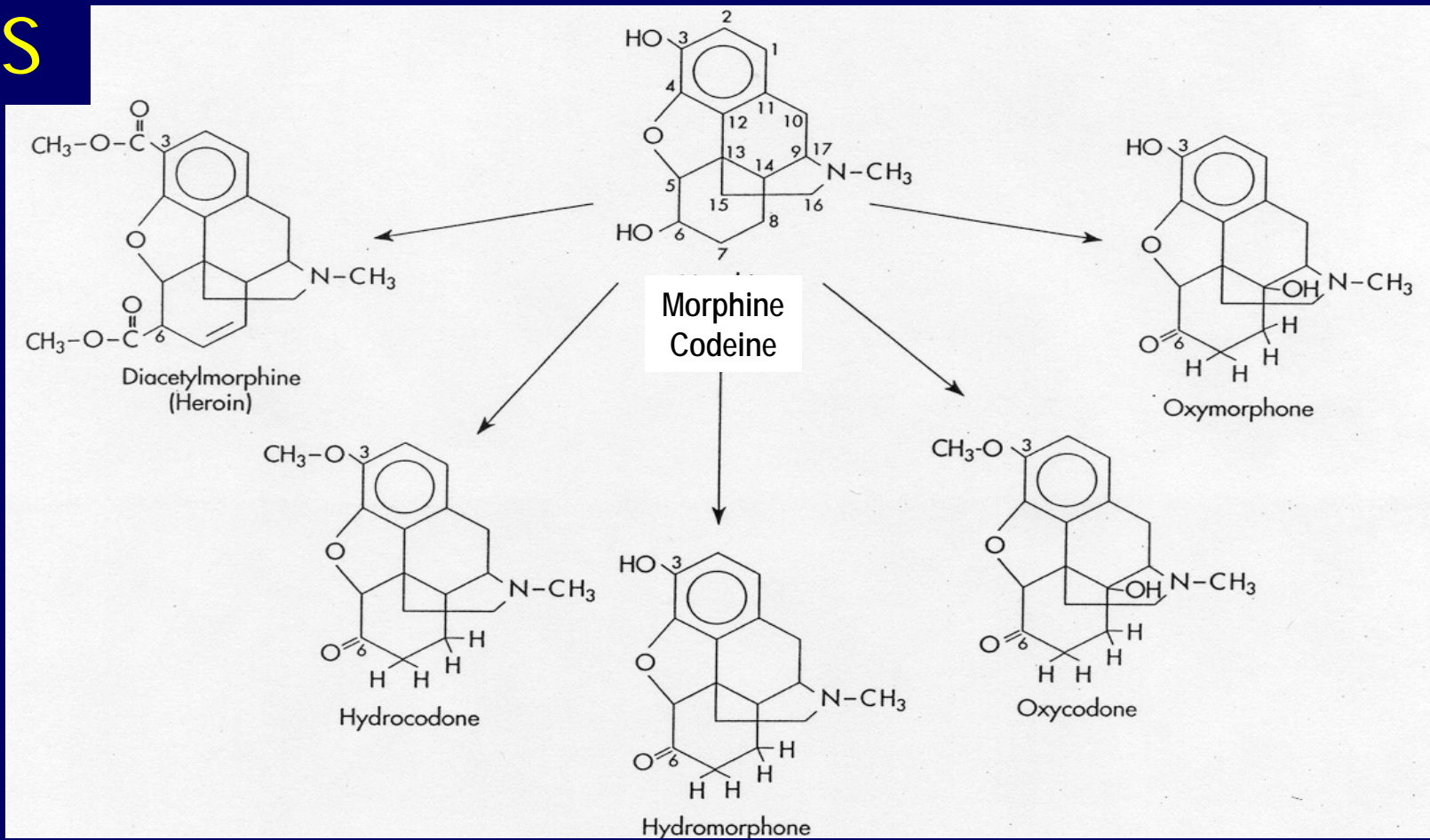


# Differential Diagnosis

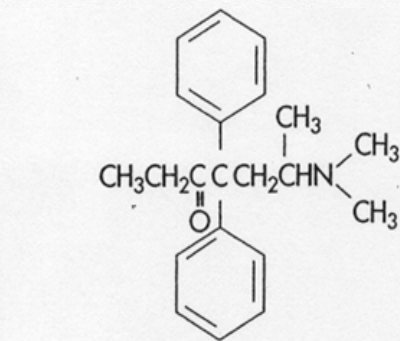
- Illicit opioid (heroin) use
- Heroin use prior to admission (*48-72 hrs*)
- Morphine given for pain last night
- Poppy seed bagel
- NOT due to methadone

# Opioids

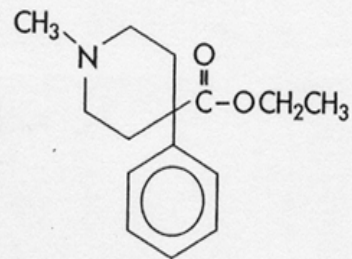
Natural  
&  
Semisynthetic



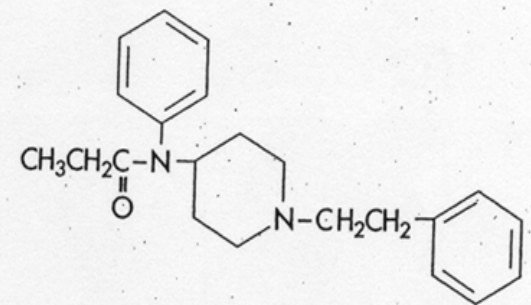
Synthetic



Methadone.



Meperidine.



Fentanyl.

# Inpatient Long-term Goals

- Referral to substance abuse treatment
  - Detoxification program leading to long term medication-free treatment (e.g. residential treatment, intensive outpatient treatment)
  - Medication assisted treatment (e.g. methadone, buprenorphine, naltrexone)

## ***6 months later***

- She presents to your primary care clinic requesting treatment for her heroin addiction
- She has been using heroin since the day she left the hospital
- She has had no additional complications from her drug use

## *Case continued*

- Recommended options from primary care
  - Narcotics Anonymous (NA)
  - Clonidine + NSAID + benzodiazepine + ...
  - Naltrexone (po or injectable)
  - Buprenorphine maintenance (if waived)
  - Referral
    - Detoxification program
    - Needle exchange
    - Acupuncture
    - Outpatient counseling
    - Methadone maintenance
    - Buprenorphine maintenance (if not waived)

# Opioid Detoxification Outcomes

- Low rates of retention in treatment
- High rates of relapse post-treatment
  - < 50% abstinent at 6 months
  - < 15% abstinent at 12 months
  - Increased rates of overdose due to decreased tolerance

O'Connor PG JAMA 2005  
Mattick RP, Hall WD. Lancet 1996  
Stimmel B et al. JAMA 1977

# Reasons for Relapse

- Protracted abstinence syndrome
  - Secondary to derangement of endogenous opioid receptor system
  - Symptoms
    - Generalized malaise, fatigue, insomnia
    - Poor tolerance to stress and pain
    - Opioid craving
- Conditioned cues (triggers)
- Priming with small dose of drug



# Methadone Maintenance Over 40 Years of Experience...

## A Medical Treatment for Diacetylmorphine (Heroin) Addiction

A Clinical Trial With Methadone Hydrochloride

Vincent P. Dole, MD, and Marie Nyswander, MD

A group of 22 patients, previously addicted to diacetylmorphine (heroin), have been stabilized with oral methadone hydrochloride. This medication appears to have two useful effects: (1) relief of narcotic hunger, and (2) induction of sufficient tolerance to block the euphoric effect of an average illegal dose of diacetylmorphine. With this medication, and a comprehensive program of rehabilitation, patients have shown marked improvement; they have returned to school, obtained jobs, and have become reconciled with their families. Medical and psychometric tests have disclosed no signs of toxicity, apart from constipation. This treatment requires careful medical supervision and many social services. In our opinion, both the medication and the supporting program are essential.

ough review of evidence available in 1957,<sup>1</sup> concluded that "The advisability of establishing clinics or some equivalent system to dispense opiates to addicts cannot be settled on the basis of objective facts. Any position taken is necessarily based in part on opinion, and on this question opinions are divided." With respect to previous trials of maintenance treatment, the Council found that "Assessment of the operations of the narcotic dispensaries between 1919 and 1923 is difficult because of the paucity of published material. Much of the small amount of data that is available is not sufficiently objective to be of great value in formulating any clear-cut opinion of the purpose of the clinics, the way in which they operated, or the results attained." No new studies bearing on the question



MEDICAL NEWS  
& PERSPECTIVES

## Methadone Treatment Marks 40 Years

Bridget M. Kuehn

**F**ORTY YEARS AND COUNTLESS political firestorms after it was first introduced, methadone maintenance for the treatment of opioid addiction remains a standard therapy in the field of addiction treatment.

The publication on August 23, 1965, of positive results from a small clinical trial of methadone as a treatment for heroin addiction in *JAMA* marked a sea change in the treatment of addiction (Dole and Nyswander. *JAMA*. 1965; 193:646-650). The study, conducted at Rockefeller University in New York City by Vincent P. Dole, MD, and the late Marie E. Nyswander, MD, suggested that a medication could be used to control the cravings and withdrawal that often lead to relapse in individuals with opioid addiction who attempt to quit.

The work, along with subsequent research by Dole, an endocrinologist, Nyswander, a psychiatrist, and colleagues established the concept of opioid addiction as a chronic disease, similar to diabetes, that as such required

now head of the Laboratory of the Biology of Addictive Diseases at Rockefeller University, explained that work conducted by the group in 1964 and published in 1966 established that methadone blocked the effects of heroin and stabilized patients, who prior to treatment oscillated between feeling

done treatment, the ap always struggled for accep the forces of public opini tics. "There is a stigma a tions, addicts, and—sadly providers," said Kreek, a supporter of the methado

### "THE FARM"

Methadone maintenance resented a reversal of the t approach to treating dru said David F. Musto, MD turer at Yale and expert policy. A 1919 Supreme sion had established th: alone did not justify phy: ing addicts with opioids. B cision, some physicians ha acting opioids to treat indi opioid addiction.

The Drug Enforcement tion, in fact, considered D illegal and had threatened him prior to the 1965 pub defy the US government wa litical courage," said Jeron who became the first natio



Ingbert Gröttinger/The Rockefeller University

JAMA 1965

JAMA 2005



# Methadone Maintenance

## Still controversial...

JAMA CLASSICS

CELEBRATING 125 YEARS

## Methadone Maintenance 4 Decades Later Thousands of Lives Saved But Still Controversial

### SUMMARY OF THE ORIGINAL ARTICLE

A Medical Treatment for Diacetylmorphine (Heroin)  
Addiction: A Clinical Trial  
With Methadone Hydrochloride

Vincent P. Dole, MD, and Marie Nyswander, MD

JAMA. 1965;193(8):646-650.

Twenty-two male patients, addicted to heroin 9.5 years (median), were stabilized using oral methadone hydrochloride and then observed for approximately 1 to 15 months (median, 3 months). The medication had 2 main effects: (1) relief of narcotic hunger (craving); and (2) induction of sufficient tolerance to block the average illegal dose of heroin.

A combination of the methadone treatment and a comprehensive program of rehabilitation was associated with marked improvement in patient problems such as jobs, returning to school, and family reconciliation. No adverse effect other than constipation was found.

The authors note that "careful medical supervision and many social services" were necessary and stressed that "both the medication and supporting program were essential." The small size of the group studied and short duration of the follow-up would best describe this as a promising and exciting but preliminary report.

See [www.jama.com](http://www.jama.com) for full text of the original JAMA article.

Commentary by Herbert D. Kleber, MD

Heroin became the street narcotic of choice. During World

**BOSTON Herald**  
WEDNESDAY, SEPTEMBER 7, 2005 \$ 50 CENTS (75 CENTS 30 MILES OUTSIDE BOSTON)

**ELEGANT FASHIONS**  
SEE PAGE 36

**Truckers punch in at drug clinic before work**

**BIG DIG JUNKIES**

IN A FIX: A line forms early in the morning outside a detox center on Topeka Street in Boston, where numerous Big Dig workers go to get a daily methadone dose.

**HERALD EXCLUSIVE: PAGE 2**

**GETTING OUT:**  
A U.S. Navy search and rescue swimmer comforts a victim of Hurricane Katrina pulled from a rooftop in New Orleans as they fly to safety aboard a Navy helicopter yesterday.

**KATRINA COVERAGE: PAGES 4-6, 25**

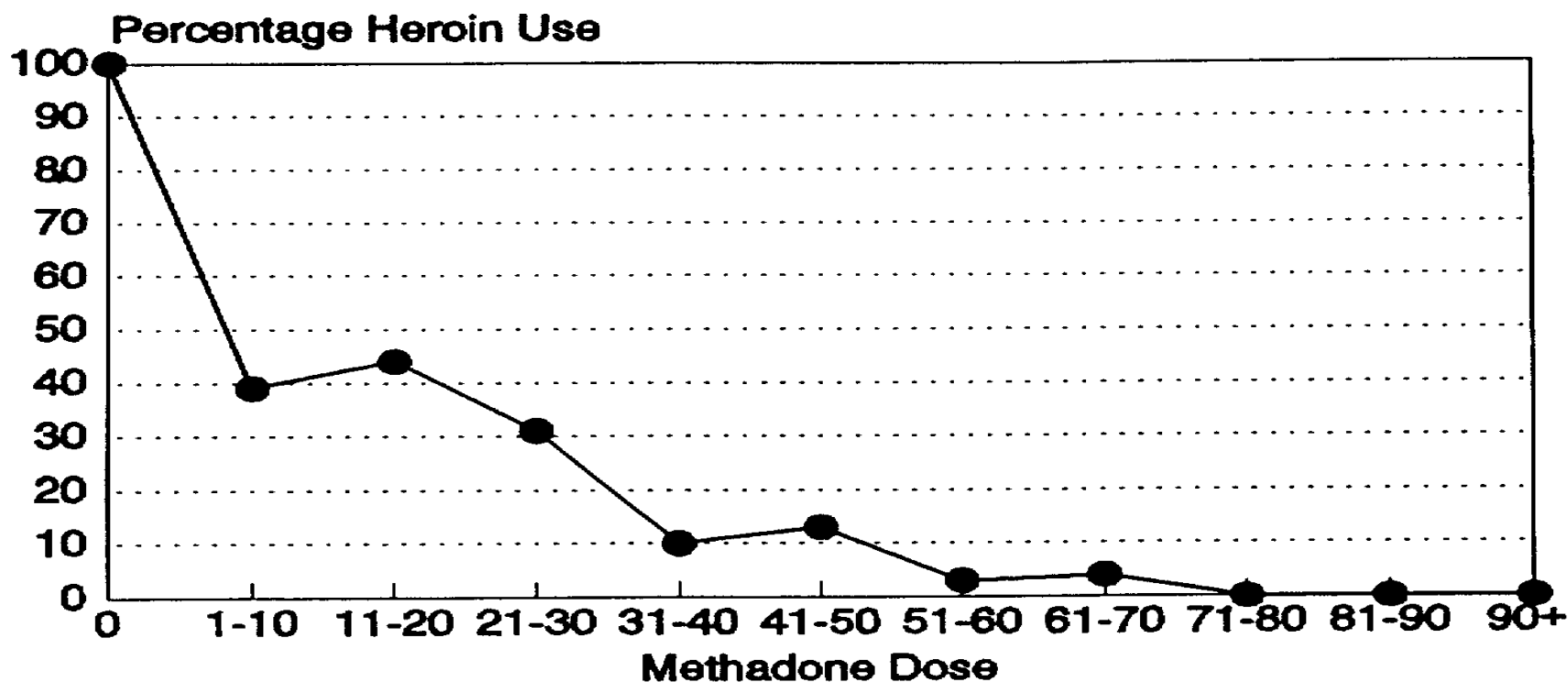
**Cape refugee plans on hold**

# Maintenance Medication Goals

- Alleviate physical withdrawal (*low doses*)
- “Narcotic blockade” (*higher doses*)
- Alleviate drug craving (*higher doses*)
- Normalized deranged brain changes
- Normalized deranged physiology

# Methadone Maintenance Dosing

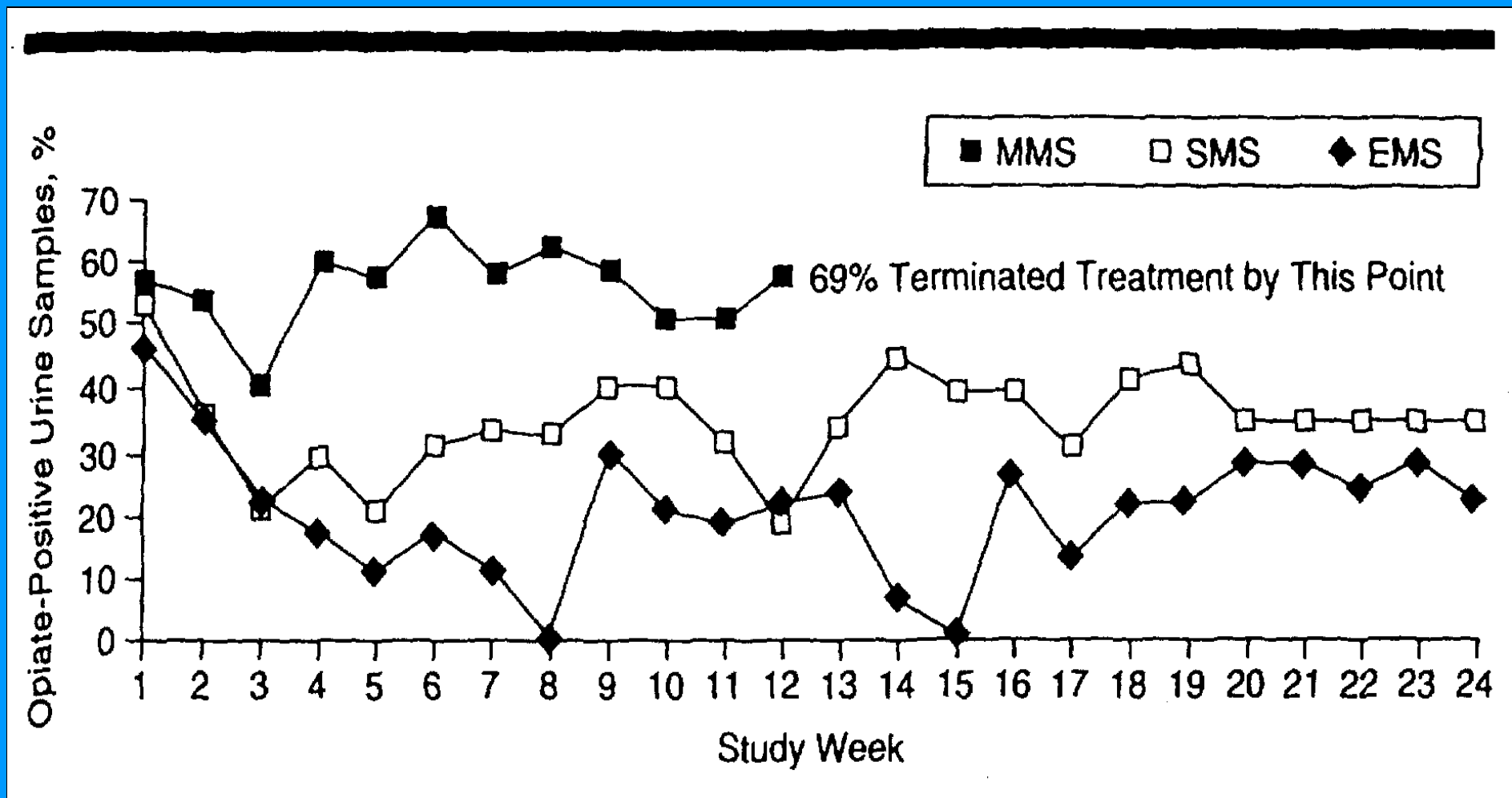
**Figure 1 - Heroin Use In Past 30 Days  
407 MM Patients by Current Methadone Dose**



SOURCE: Ball and Ross 1991, p. 248.

\* Adapted from a study of 407 methadone maintenance patients.

# Effects of Psychosocial Services



McLellan, AT et.al , J AMA 1993

# Methadone Maintenance Treatment

## Highly Structured

- Daily nursing assessment
- Weekly individual and/or group counseling
- Random supervised toxicology screens
- Psychiatric services
- Medical services
- Methadone dosing
  - Observed daily  $\Rightarrow$  “Take homes”

# In a Comprehensive Rehabilitation Program...

- Increases overall survival
- Increases treatment retention
- Decreases illicit opioid use
- Decreases hepatitis and HIV seroconversion
- Decreases criminal activity
- Increases employment
- Improves birth outcomes

# Methadone Maintenance Limitations

- Highly regulated - *Narcotic Addict Treatment Act 1974*
  - Created methadone clinics (Opioid Treatment Programs)
  - Separate system not involving primary care or pharmacists
- Limited access
- Inconvenient and highly punitive
- Mixes stable and unstable patients
- Lack of privacy
- No ability to “graduate” from program
- Stigma

# DATA 2000 and Buprenorphine

## **2000:** Drug Addiction Treatment Act (DATA) 2000

- Allows qualified physician to prescribe scheduled III - V, narcotic FDA approved for opioid maintenance or detoxification treatment limit 30 patients per practice

**2002:** Suboxone and Subutex FDA approved

**2005:** Limit to 30 patients per physician

**2007:** Limit to 100 patients per physician after 1 year



# Physician Qualifications

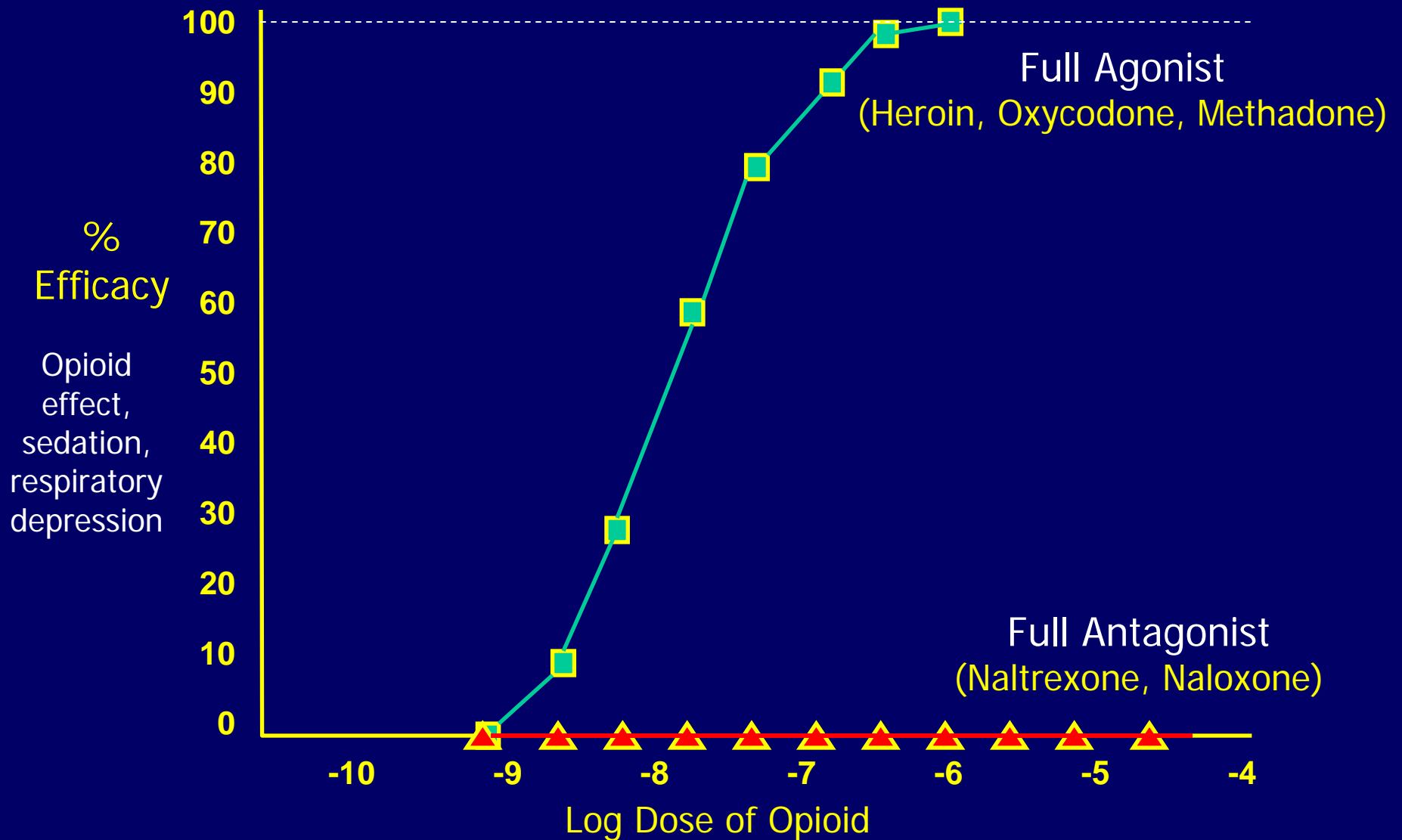
The physician is licensed under State law and “qualified” based on one of the following:

- Certified in Addiction Psychiatry or Medicine
- Completed eight hours of training
  - List of trainings: [www.buprenorphine.samhsa.gov](http://www.buprenorphine.samhsa.gov)
  - Online training:

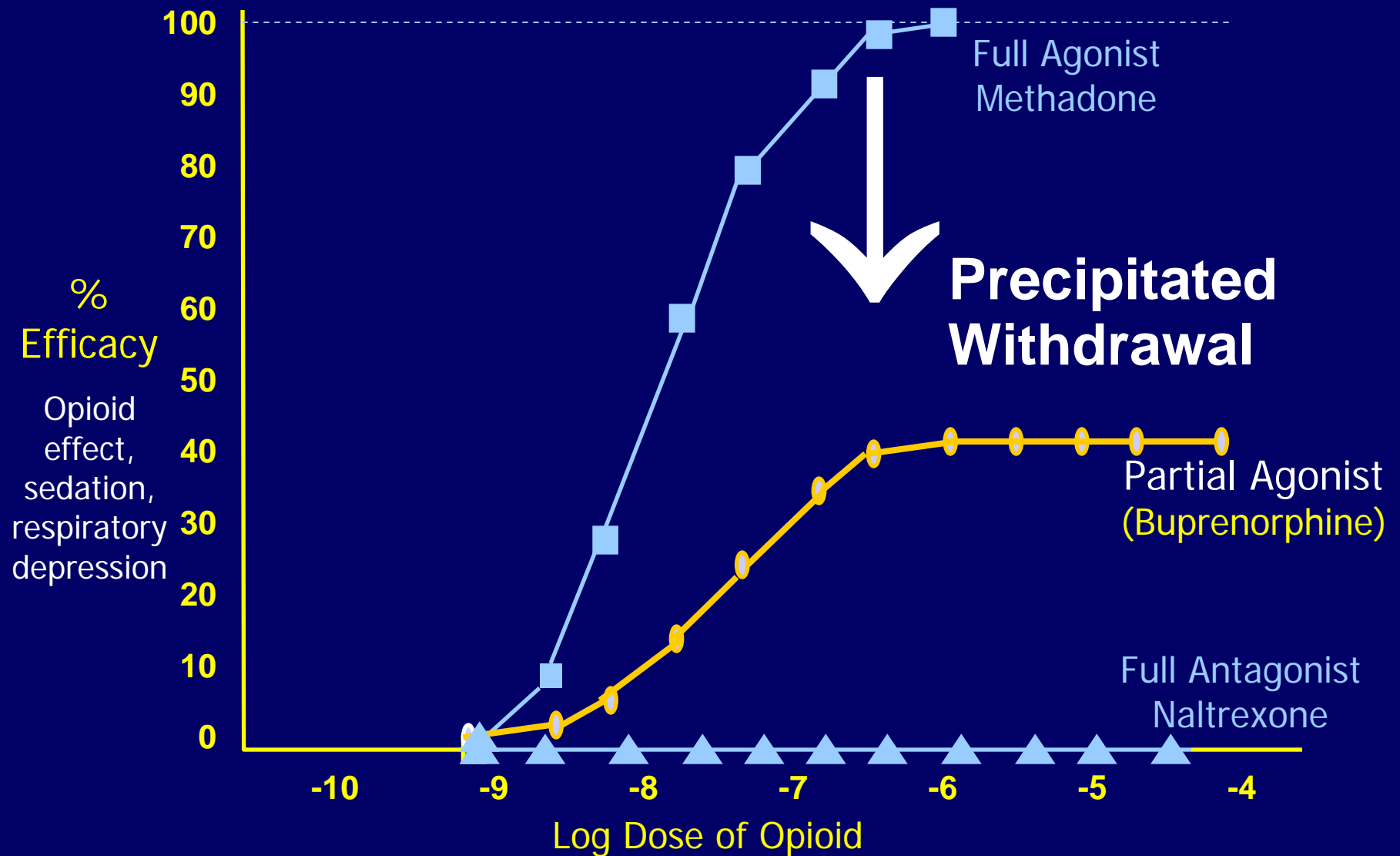


The screenshot shows the BuprenorphineCME.com website. At the top, the site name "BuprenorphineCME.com" is displayed in a large, bold, red font. Below the site name is a horizontal navigation bar with several red buttons containing white text: "Home", "Course List", "Resources", "Help", "About Us", "Contact Us", and "Sign Up Now!". Below the navigation bar is a login section with a red background. It contains the labels "User Name" and "Password" in white text, followed by white input fields. To the right of the input fields is a white button with the text "Login" in red.

# Opioid Potency

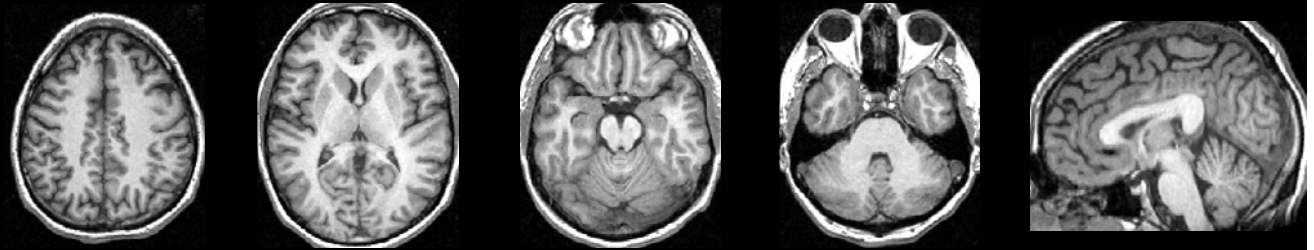


# Buprenorphine: Ceiling Effect

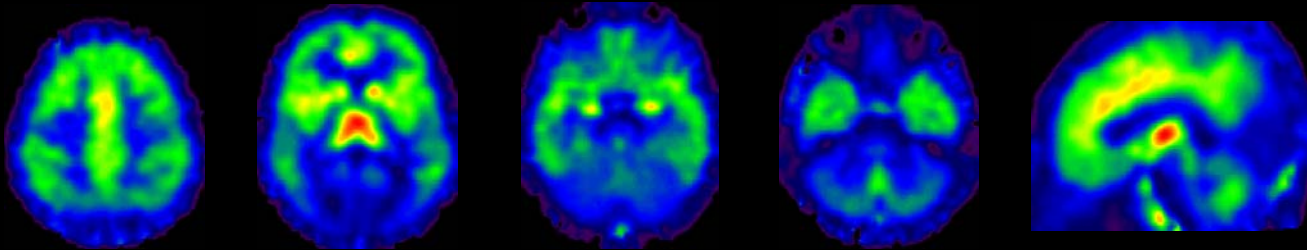


# Effects of Buprenorphine Dose on *mu* Receptor Availability

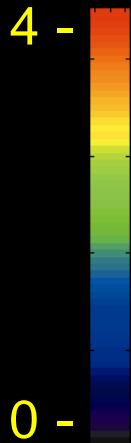
**MRI**



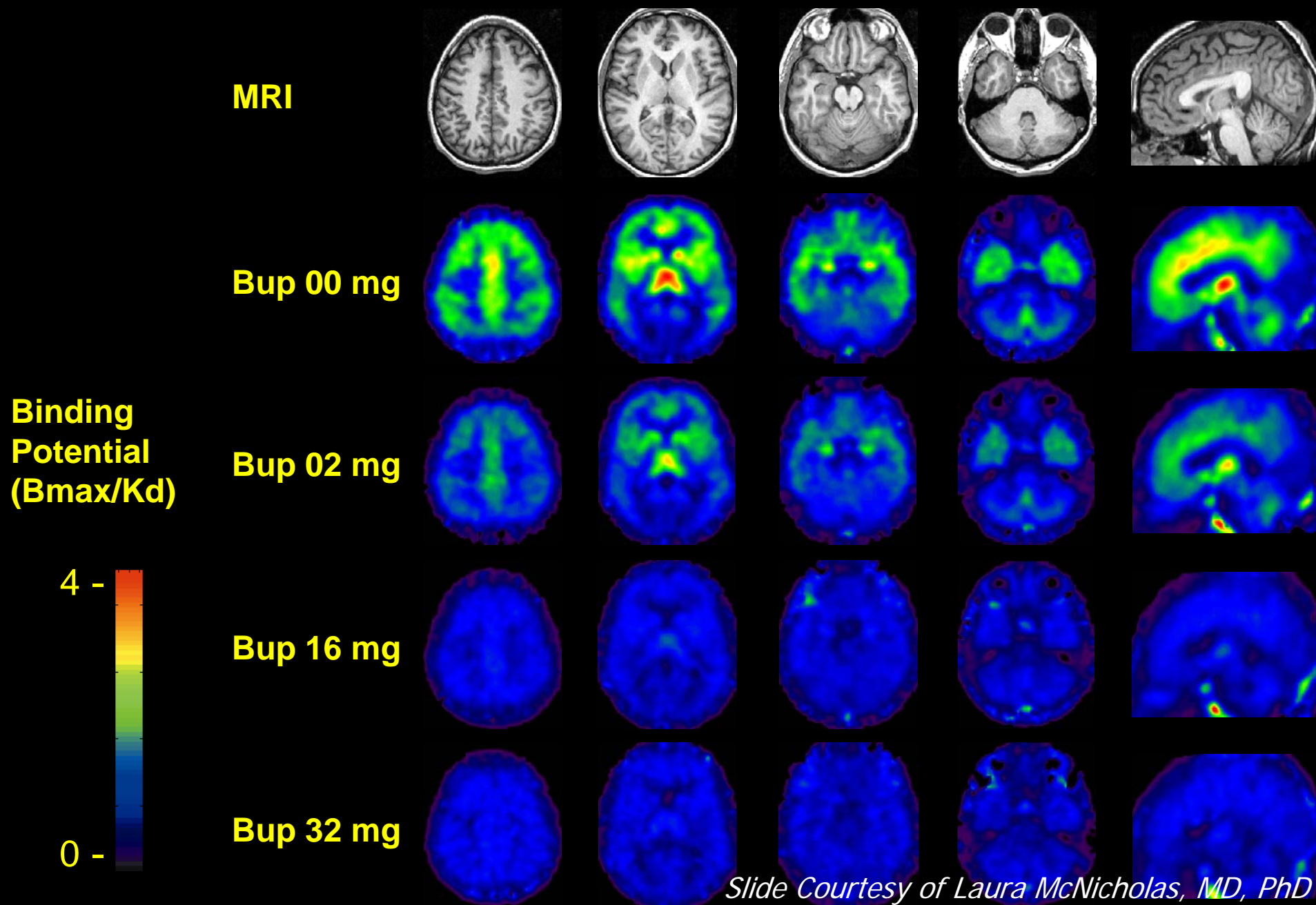
**Bup 00 mg**



**Binding  
Potential  
(Bmax/Kd)**



# Effects of Buprenorphine Dose on *mu* Receptor Availability



*Slide Courtesy of Laura McNicholas, MD, PhD*

# Buprenorphine Pharmacology

- Subutex<sup>®</sup> (“*mono*”)
- Suboxone<sup>®</sup> (“*combo*”) *buprenorphine + naloxone*
  - Schedule III
  - Sublingual tablets
  - Treatment of opioid dependence
  - High receptor affinity
  - Slow dissociation
  - Ceiling effect for respiratory depression but not analgesia



# Buprenorphine Efficacy

- Studies (RCT) show buprenorphine more effective than placebo and equally effective to moderate doses (80 mg) of methadone on primary outcomes of:
  - Abstinence from illicit opioid use
  - Retention in treatment
  - Decreased opioid craving

Johnson et al. NEJM 2000

Fudala PJ et al. NEJM 2003

Kakko J et al. Lancet 2003

# Question....

- **How long should a patient remain on medication (e.g. methadone, buprenorphine) maintenance therapy?**
- **Answer: Long enough.**



# Opioid Maintenance Treatment and Acute Pain Management

- Patients on opioid maintenance treatment (i.e. methadone or buprenorphine) have less pain tolerance than matched controls
- Patients who are physically dependent on opioids (i.e. methadone or buprenorphine) must be maintained on daily equivalence before ANY analgesic effect is realized with opioids used for acute pain management
- Opioid analgesic requirements are often higher due to increased pain sensitivity and opioid cross tolerance

Alford DP, Compton P, Samet JH. Ann Intern Med 2006

# Summary 1

- Heroin overdose is common in experienced users
- High risk period when tolerance is low
- For patients with active opioid addiction, not enrolled in maintenance treatment, treat acute opioid withdrawal during hospitalization with methadone 20-40mg to facilitate full medical/surgical treatment
- For patients enrolled in maintenance treatment, confirm and then continue maintenance dose during hospitalization

# Summary 2

- Methadone maintenance, highly structured, with many years of proven efficacy, but w/ limitations
- Buprenorphine maintenance in office-based settings, less structured, as effective as moderate dose methadone w/ fewer limitations
- Patients with history of opioid dependence, including those on opioid agonist maintenance, have lower pain tolerance
- Acute pain management requires continuation of maintenance opioid and often times, higher doses of opioid analgesics