Opioids
Research to Practice

CRIT Program

May 2010

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

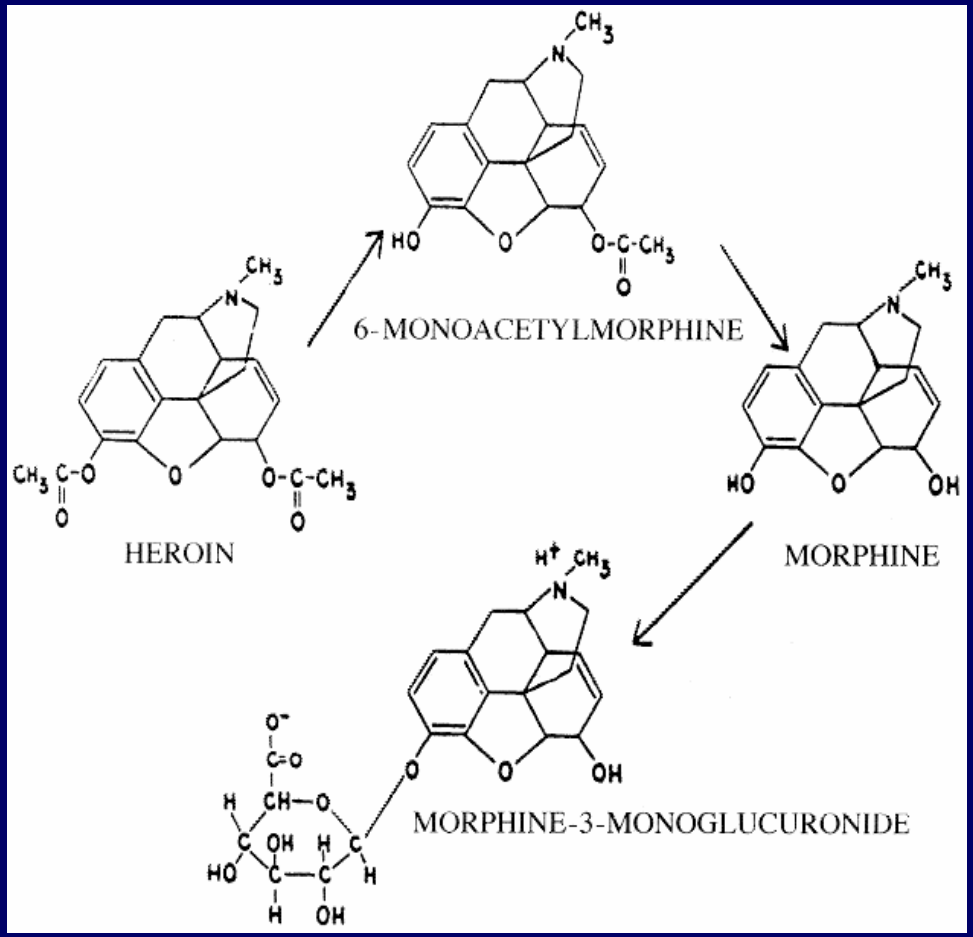
BOSTON UNIVERSITY

BOSTON MEDICAL CENTER
BOSTON UNIVERSITY SCHOOL OF MEDICINE
GENERAL INTERNAL MEDICINE

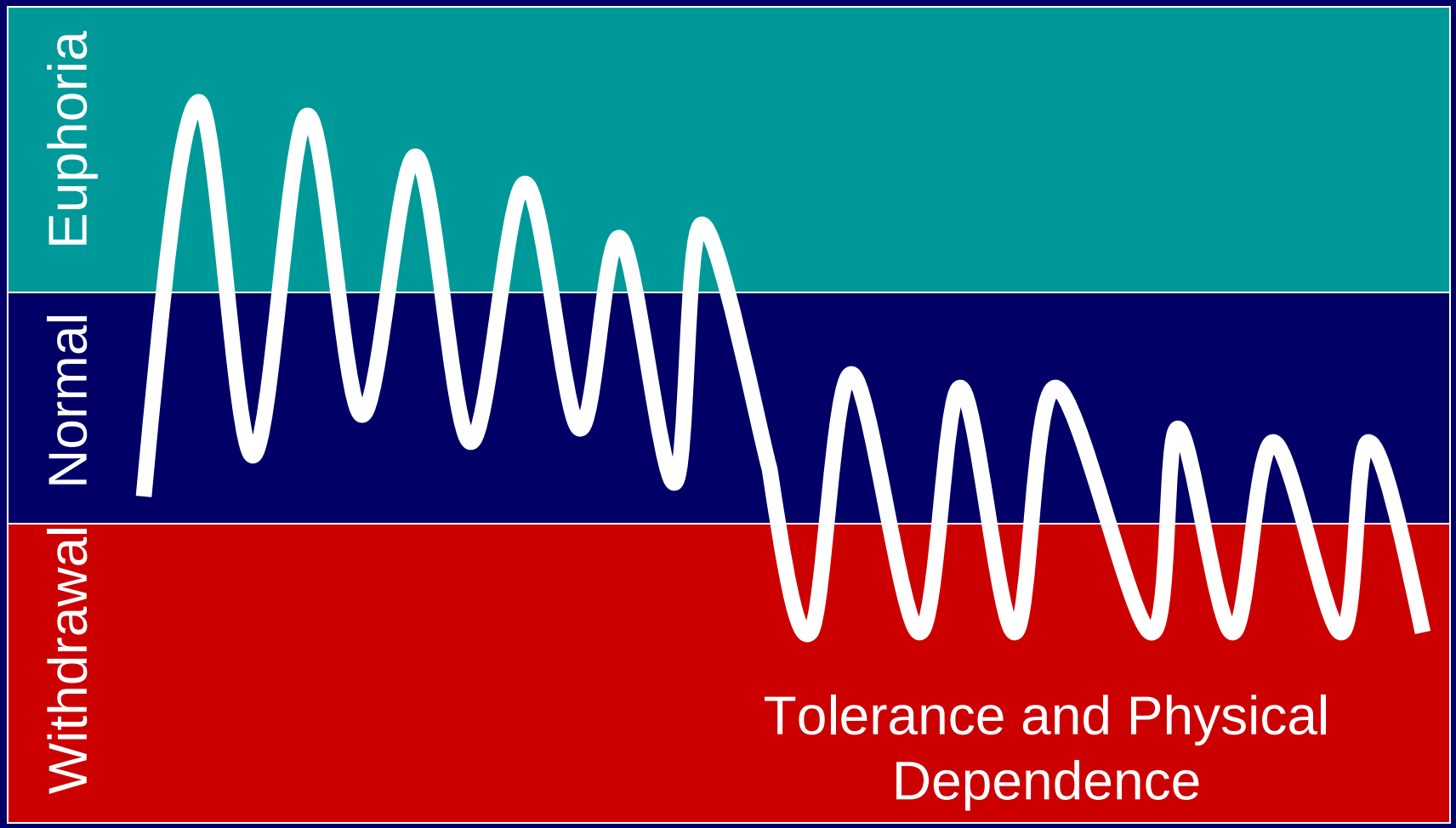
- 32 yo female brought in after “heroin overdose”
- Brisk response to IV naloxone 0.4 mg
- Re-sedation after 1 hr requiring repeat naloxone
- Arm cellulitis at injection drug use site
- Admitted for “drug overdose”, “persistent altered mental status” and “arm cellulitis”

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

Darke S. Addiction 1996, Gossop M. BMJ 1996

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 methadone or buprenorphine 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
	0	Anxiety, Drug Craving
4-6	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)*

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

Which medication(s) should be used to treat opioid withdrawal on the inpatient service?

- 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 prevent opioid withdrawal
  - 6-8 hours analgesia
- Proper dosing
  - Acute withdrawal 20-40 mg
  - Craving, “narcotic blockade” >80 mg

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

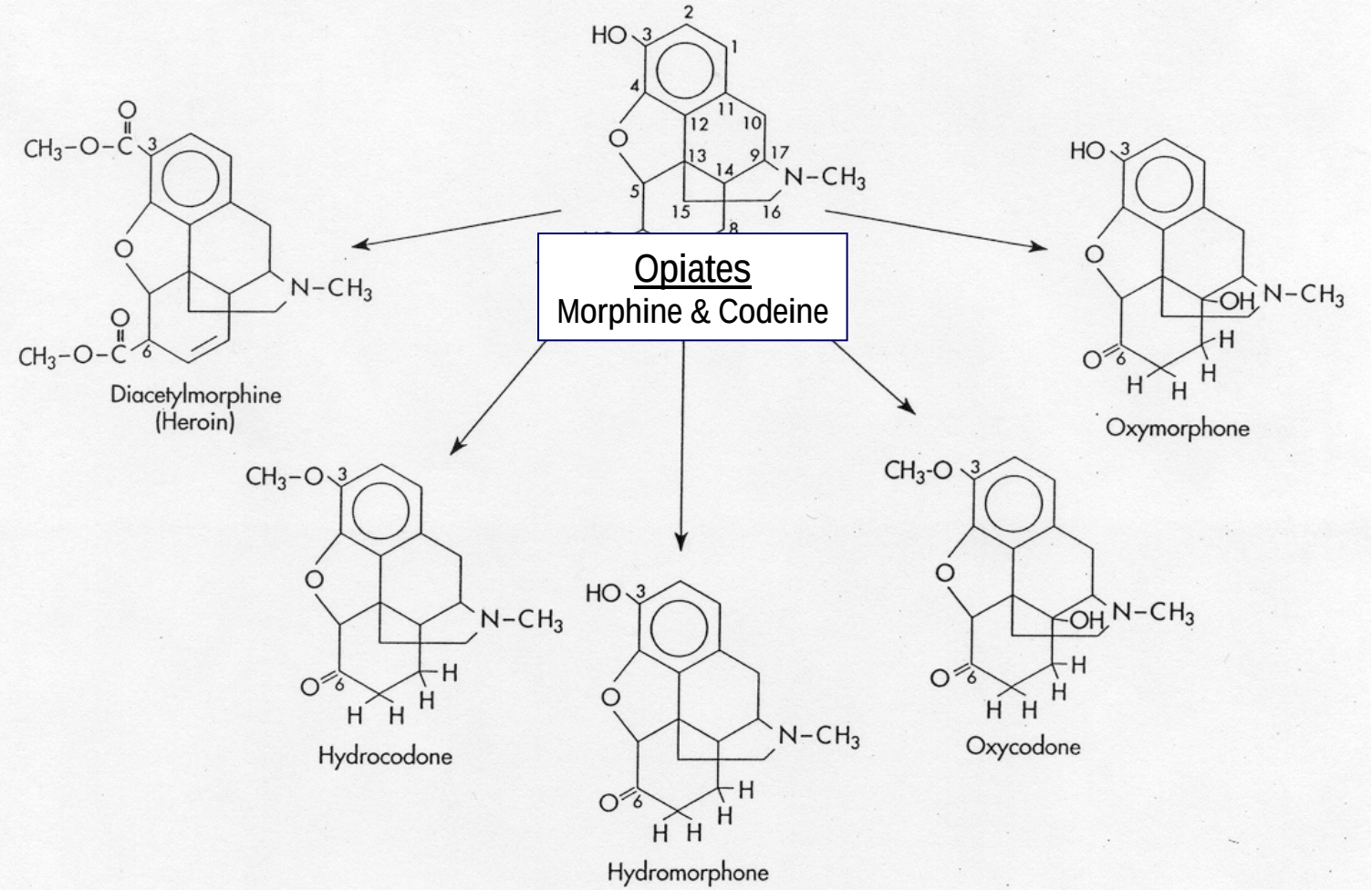
- NOT due to methadone

Opioids

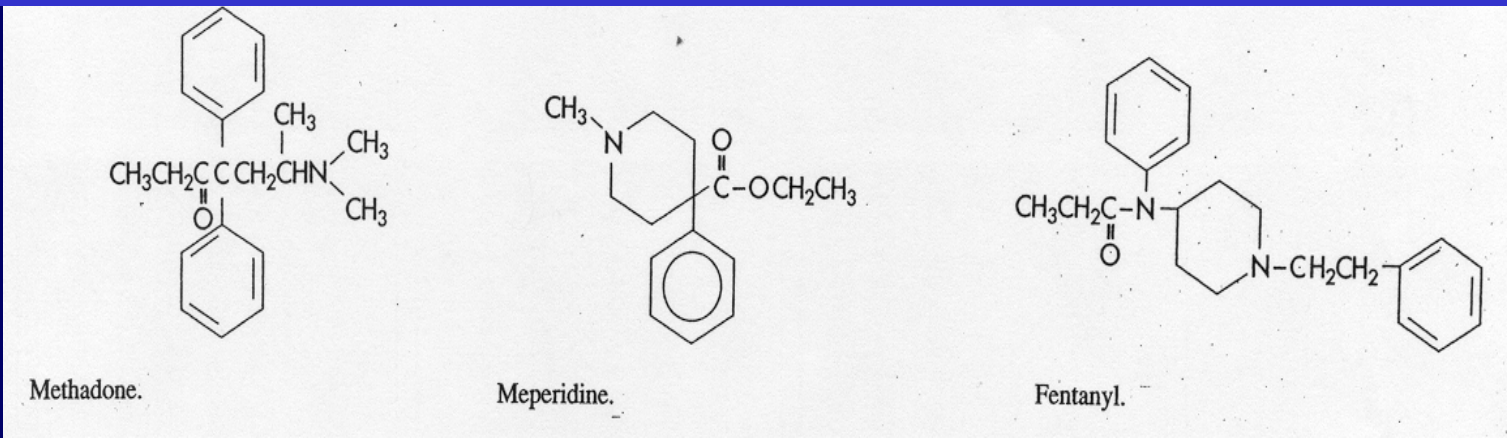
Natural (opiates)

▼

Semisynthetic



Synthetic



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)

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
  - Buprenorphine maintenance (if waivered)
  - Referral
    - Detoxification program
    - Needle exchange
    - Acupuncture
    - Outpatient counseling
    - Methadone maintenance

Treatment?... The Lexington Narcotic Farm

Opened **May 1935**, Lexington, Kentucky. 1,050-acre site included a farm and dairy, working on which was considered therapeutic for patients

With increased availability of state and local drug abuse treatment programs, the hospital was closed in **February 1974**

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

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,[1] 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

JAMA 1965

MEDICAL NEWS & PERSPECTIVES

Methadone Treatment Marks 40 Years

Bridget M. Kuehn

FORTY 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

Ingbert Grüttner/The Rockefeller University

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 methadc

"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 tha
alone did not justify phys
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

JAMA 2005

The evidence and guidelines…

Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (Review)

Mattick RP, Kimber J, Breen C, Davoli M

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

WILEY Publishers Since 1807

Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence

World Health Organization

2010

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 for full text of the original *JAMA* article.

Commentary by Herbert D. Kleber, MD

Heroin became the street narcotic of choice. During World

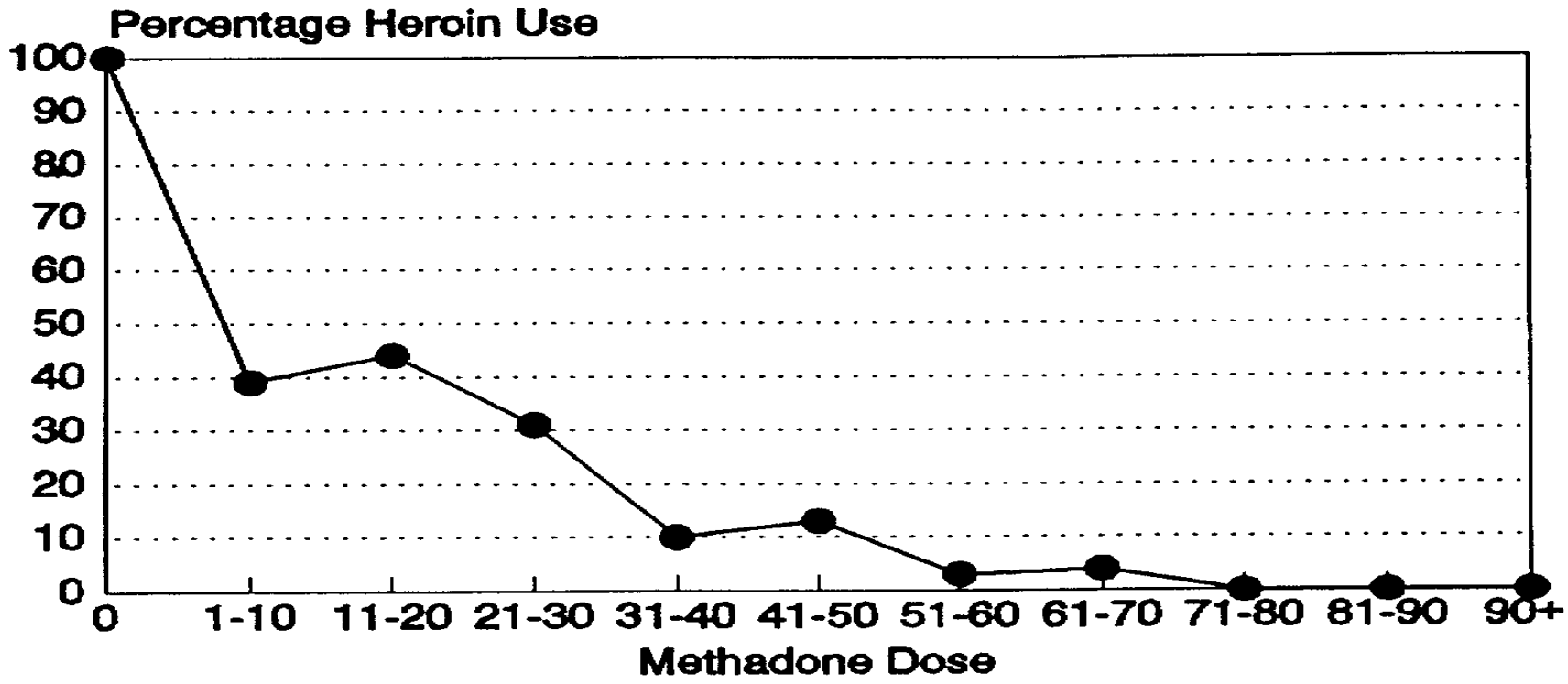
Maintenance Medication Goals

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

Dose Response

Figure 1 - Heroin Use in Past 30 Days

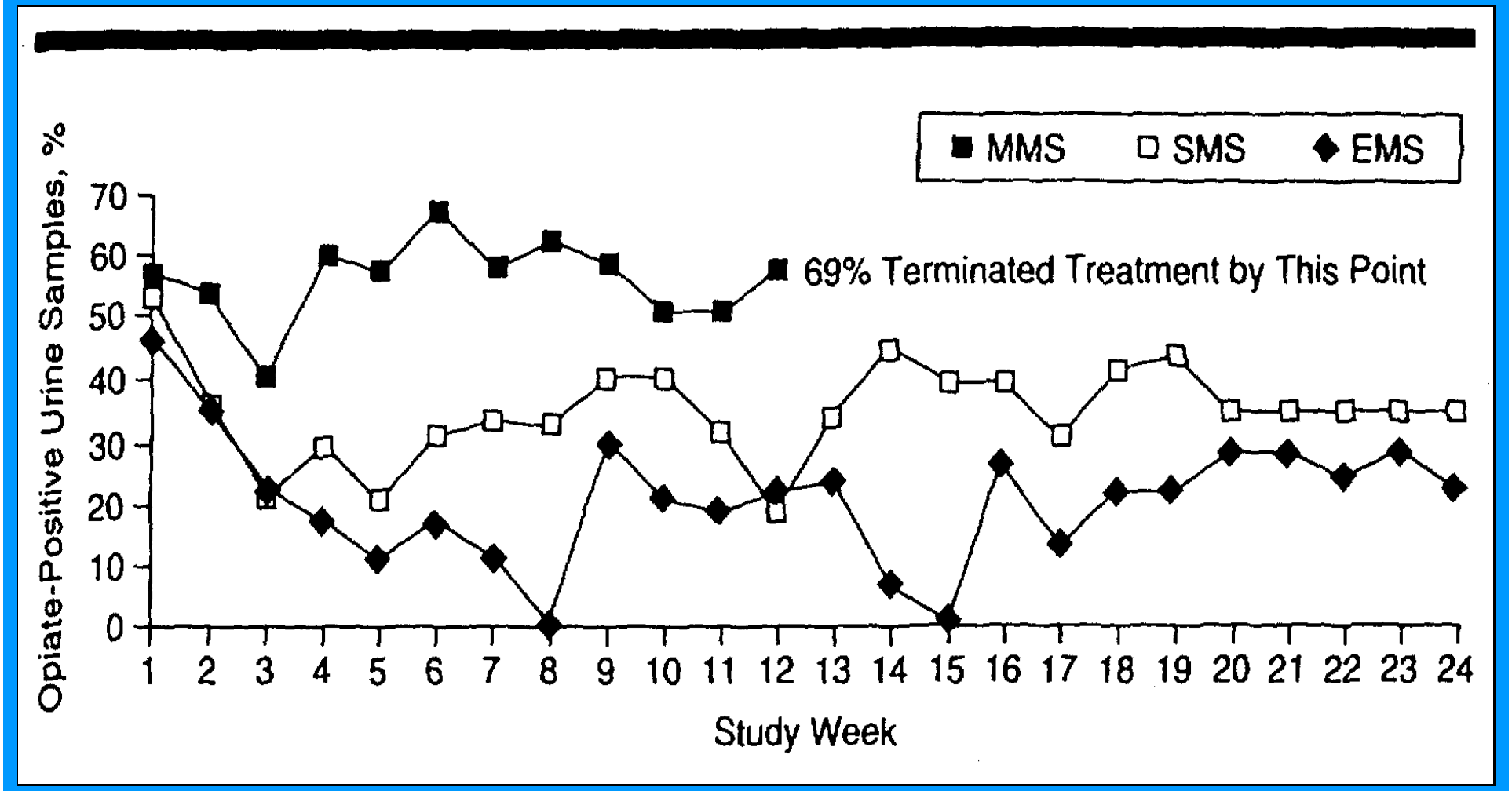
407 MM Patients by Current Methadone Dose



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 CRIT 2010

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
  - 5 states: 0 clinics, 4 states: < 3 clinics
- Inconvenient and highly punitive
- Mixes stable and unstable patients
- Lack of privacy
- No ability to “graduate” from program
- Stigma

Hospitalized Patient on Methadone Maintenance

- Confirm enrollment in methadone maintenance
- Continue maintenance dose during hospitalization
- Communicate with methadone program at time of discharge

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

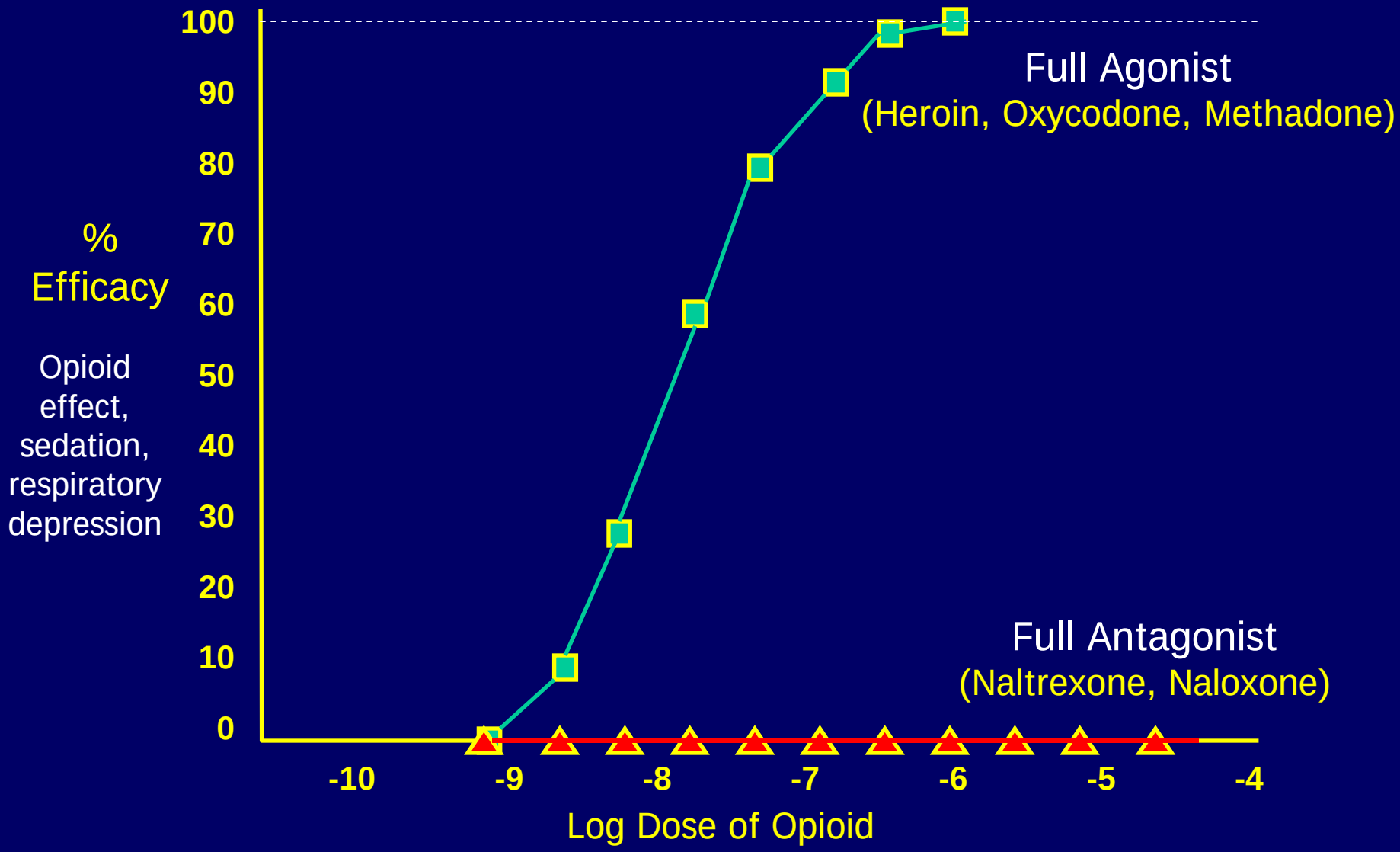
2007: Limit to 100 patients per physician after 1 year

Physician Qualifications

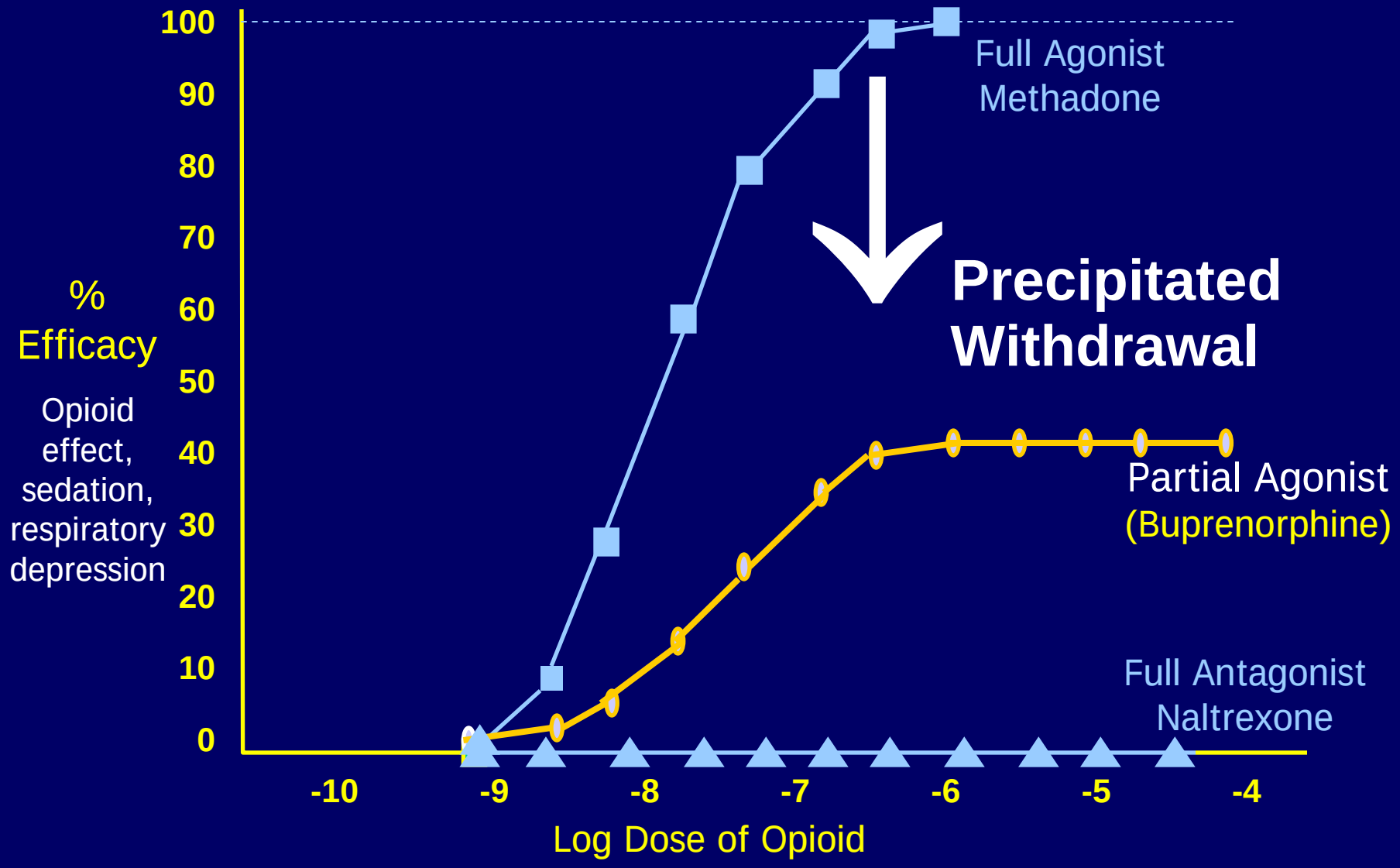
The physician is licensed under State law and "qualified" based on one of the following:

- Certified in Addiction Psychiatry or Medicine
- Completed eight hours of training
  - List of trainings: *www.buprenorphine.samhsa.gov*
  - Online training:

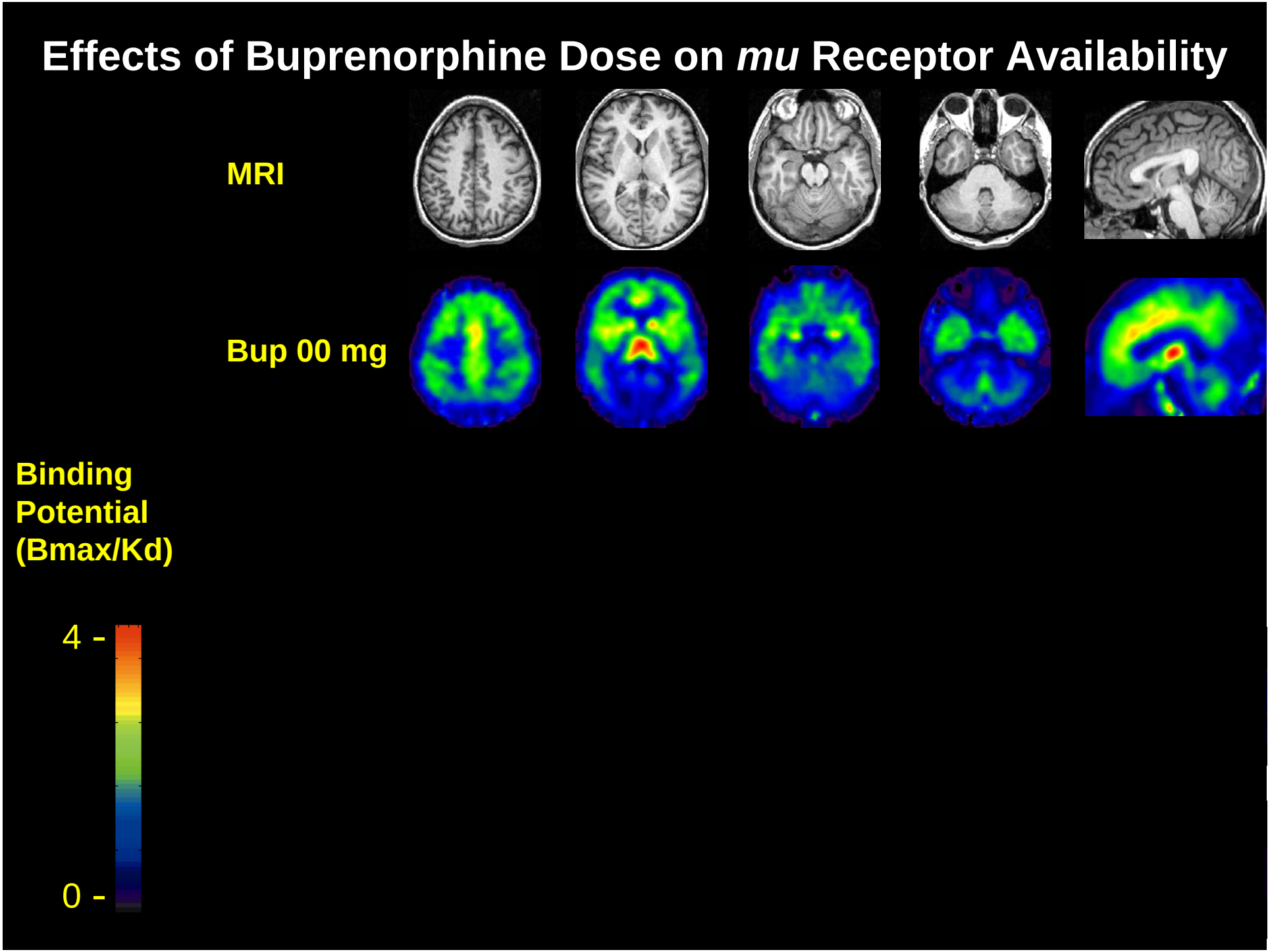
Opioid Potency



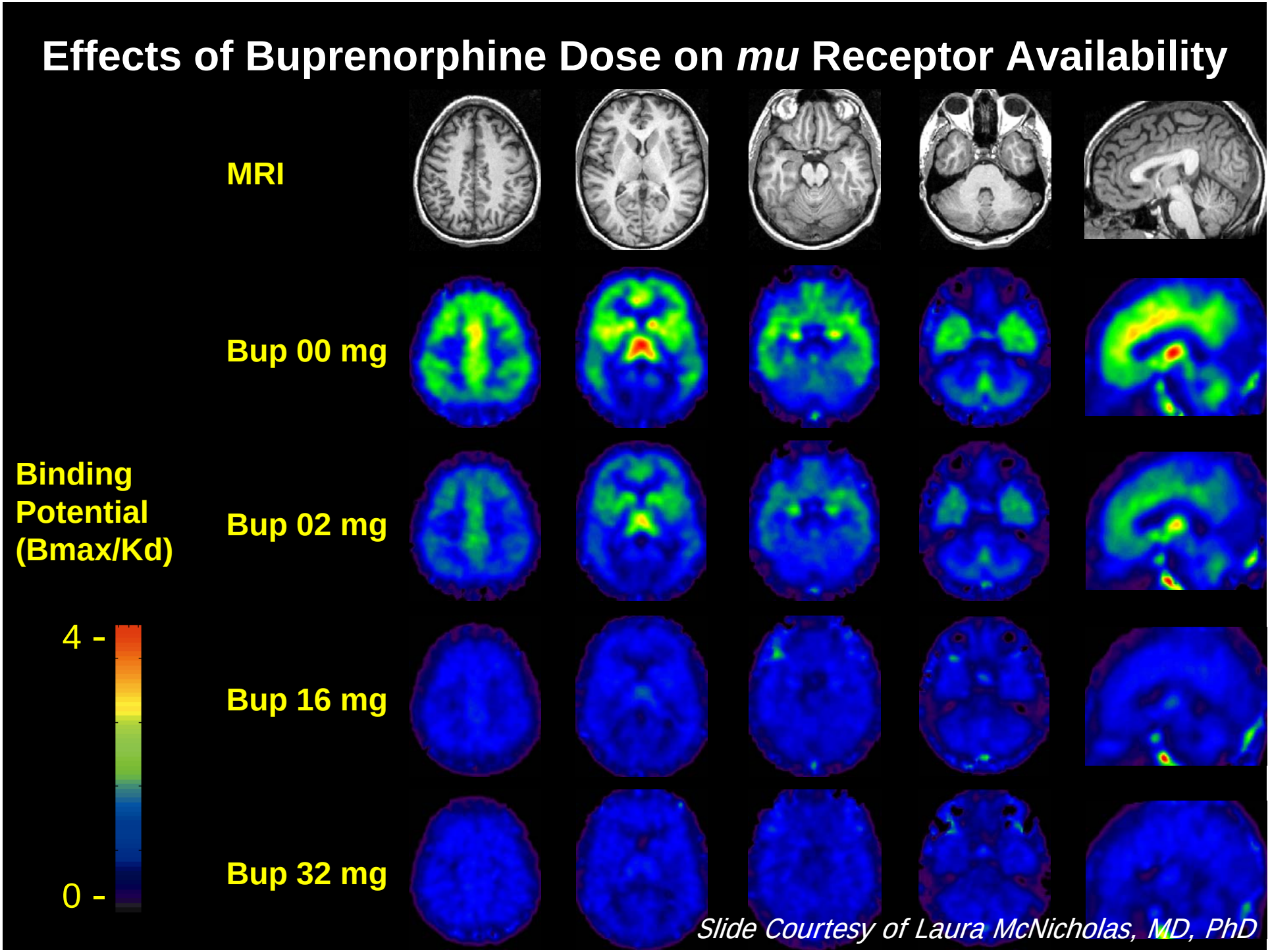
Buprenorphine: Ceiling Effect



Effects of Buprenorphine Dose on *mu* Receptor Availability

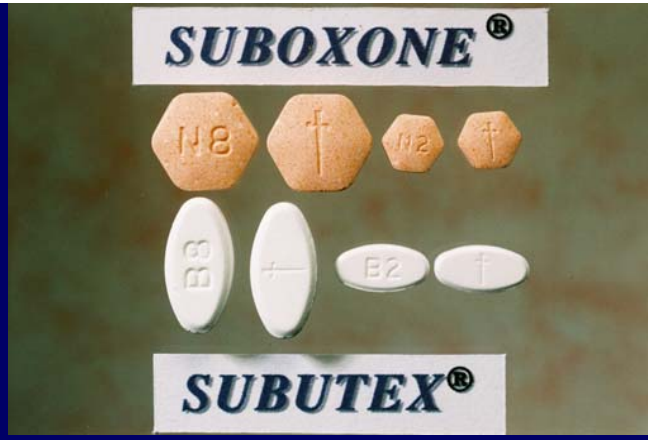


Effects of Buprenorphine Dose on *mu* Receptor Availability



Slide Courtesy of Laura McNicholas, MD, PhD

Buprenorphine Pharmacology



- Subutex® *(“mono”)*
- Suboxone®*(“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

Opioid Maintenance Treatment and Acute Pain Management

- Patients on opioid maintenance treatment (i.e. methadone or buprenorphine) have less pain tolerance then 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