Opioids
Research to Practice

CRIT/FIT 2012

May 2012

Daniel P. Alford, MD, MPH, FACP, FASAM
Associate Professor of Medicine

Boston Medical Center
Boston University School of Medicine
General Internal Medicine

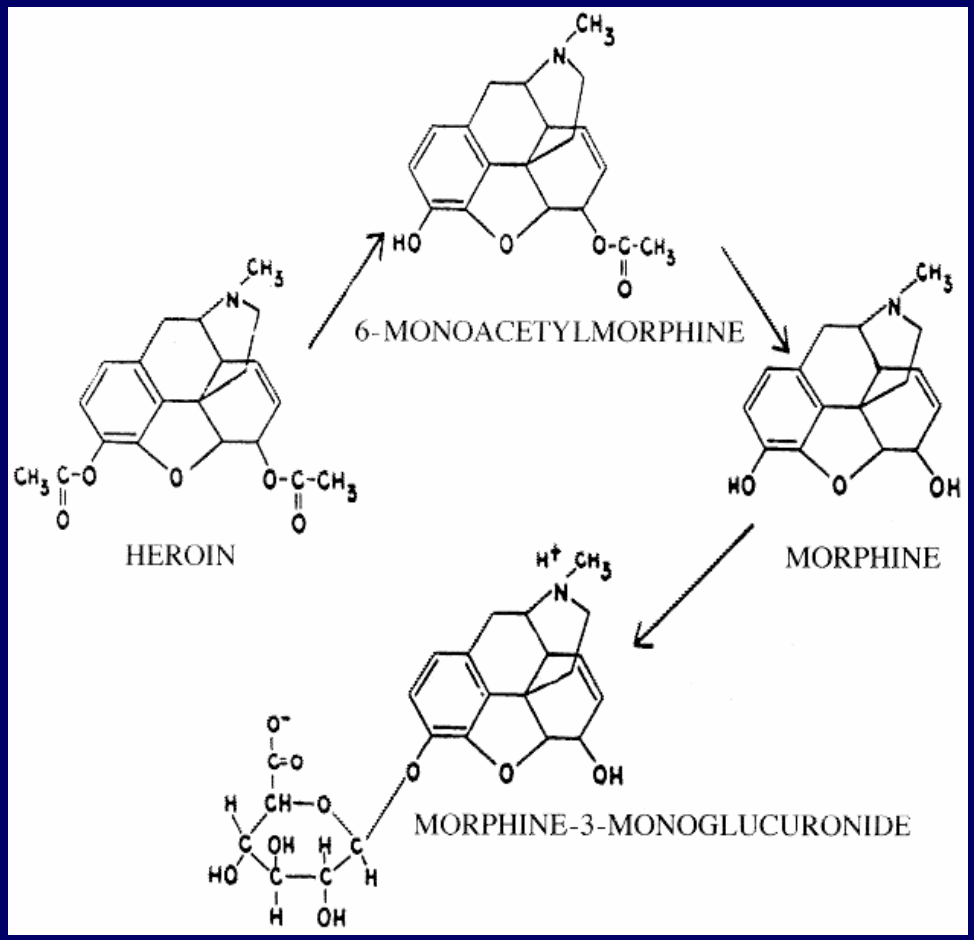
BU
Boston University School of Medicine

CARE
Clinical Addiction Research and Education

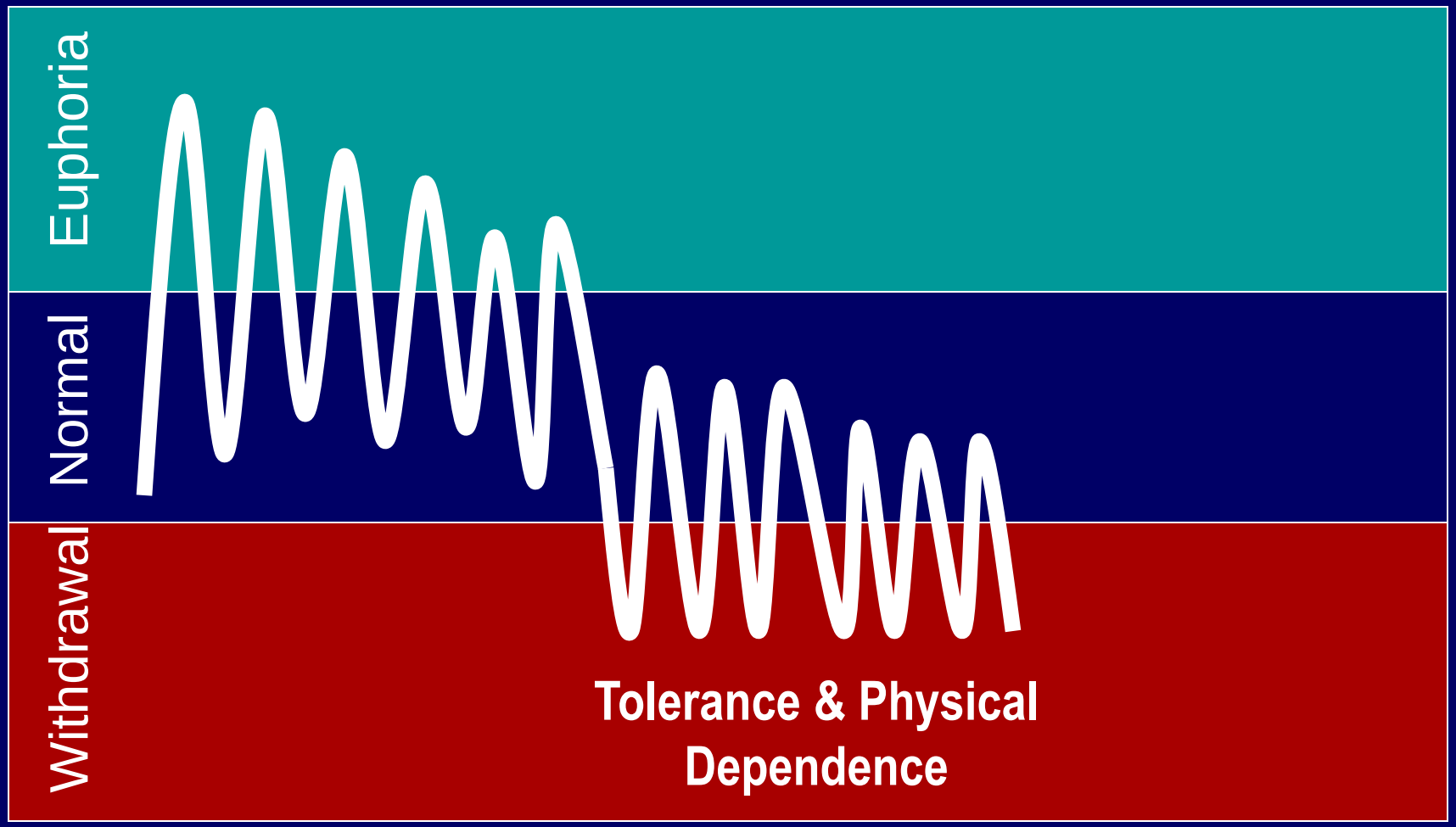
- 32 yo female brought in after “heroin overdose”
- Brisk response to IV naloxone 0.4 mg
- Re-sedation after 1 hr requiring repeat naloxone
- Arm cellulitis at injection drug use site
- Admitted for “drug overdose”, “persistent altered mental status” and “arm cellulitis”

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



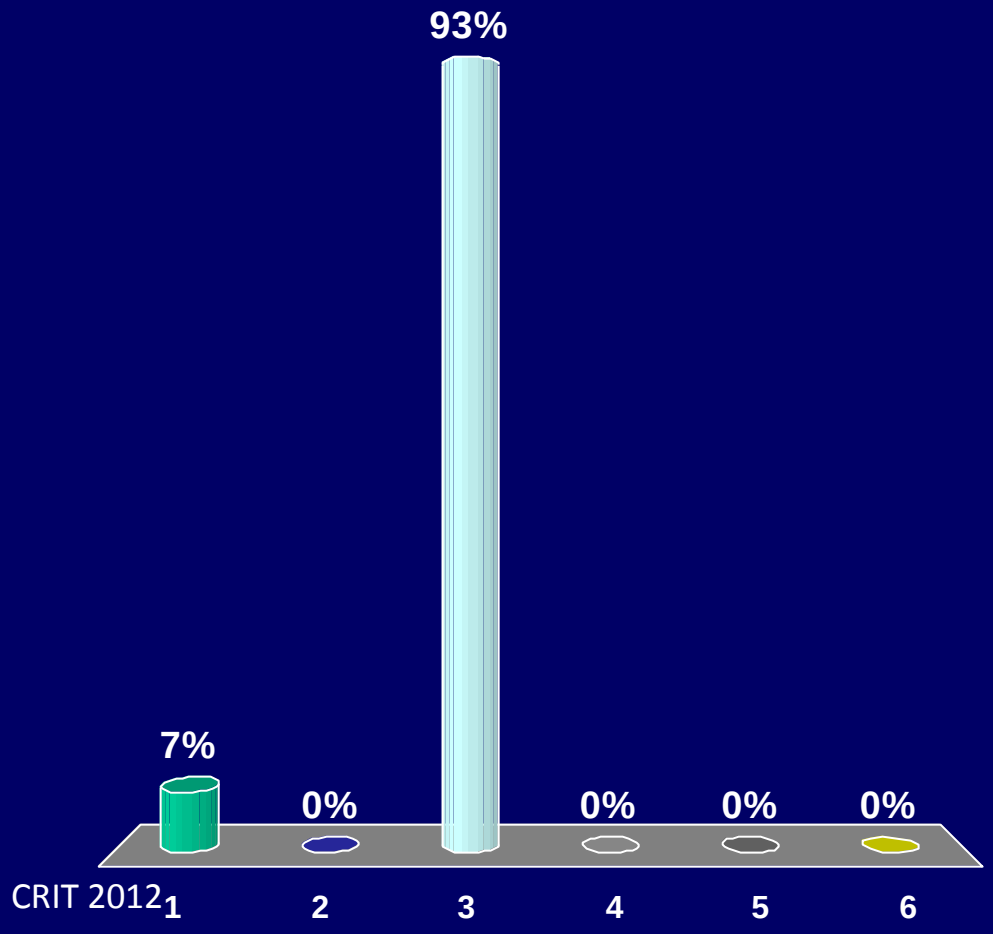
Substance abuse history

- 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
- 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?

Which is NOT a sign of opioid withdrawal?

1. Vomiting
2. Diarrhea
3. Pinpoint pupils
4. Rhinorrhea
5. Lacrimation
6. Piloerection



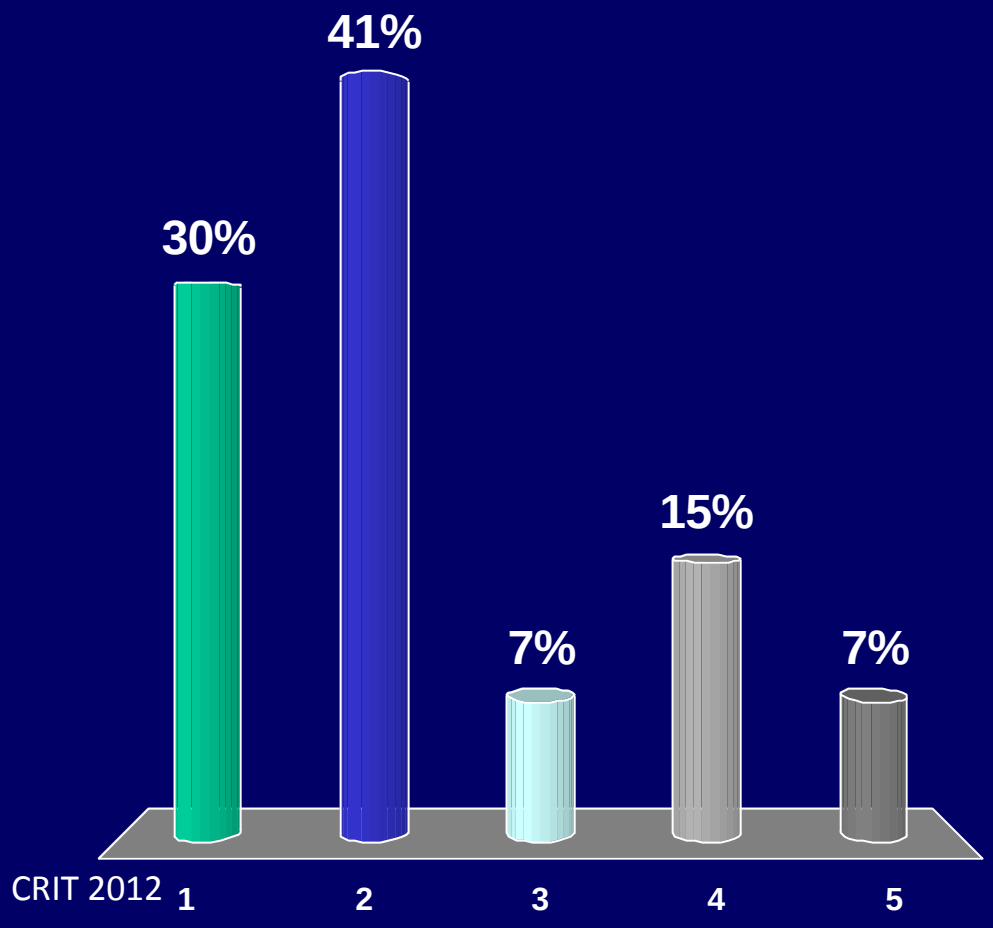
Opioid Withdrawal Assessment

Grade	Symptoms / Signs
0	Anxiety, Drug Craving
1	Yawning, Sweating, Runny nose, Tearing eyes, Restlessness Insomnia
2	Dilated pupils, Gooseflesh, Muscle twitching & shaking, Muscle & Joint aches, Loss of appetite
3	Nausea, extreme restlessness, elevated blood pressure, Heart rate > 100, Fever
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)*

How is acute opioid withdrawal treated on your inpatient service?

1. Clonidine
2. Methadone
3. Buprenorphine
4. Don't know
5. Other



Inpatient 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 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)

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 opioids
- Discuss taper vs maintained dose w/ pt daily
- Referral for long-term substance abuse treatment

Inpatient Methadone Dosing Guidelines

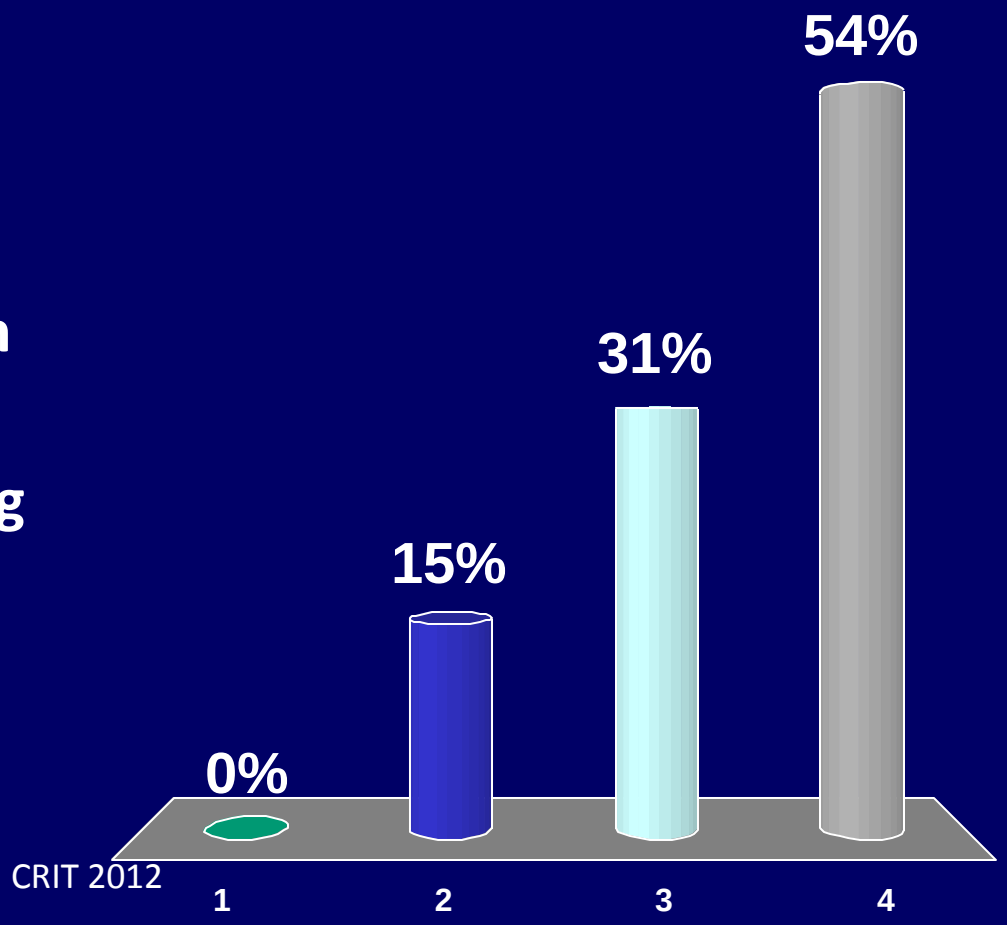
- Maintained dose option
  - Give same dose each daily including day of discharge
  - Allows 24-36 hour withdrawal-free period after d/c
- Tapered dose option
  - If patient requests a taper, decrease by 5 mg per day and stop taper if patient requests it
  - Don't prolong hospitalization to complete 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 methadone dose
    - Was off the floor for 2 hours
    - Repeat urine drug test was positive for "**opiates**"

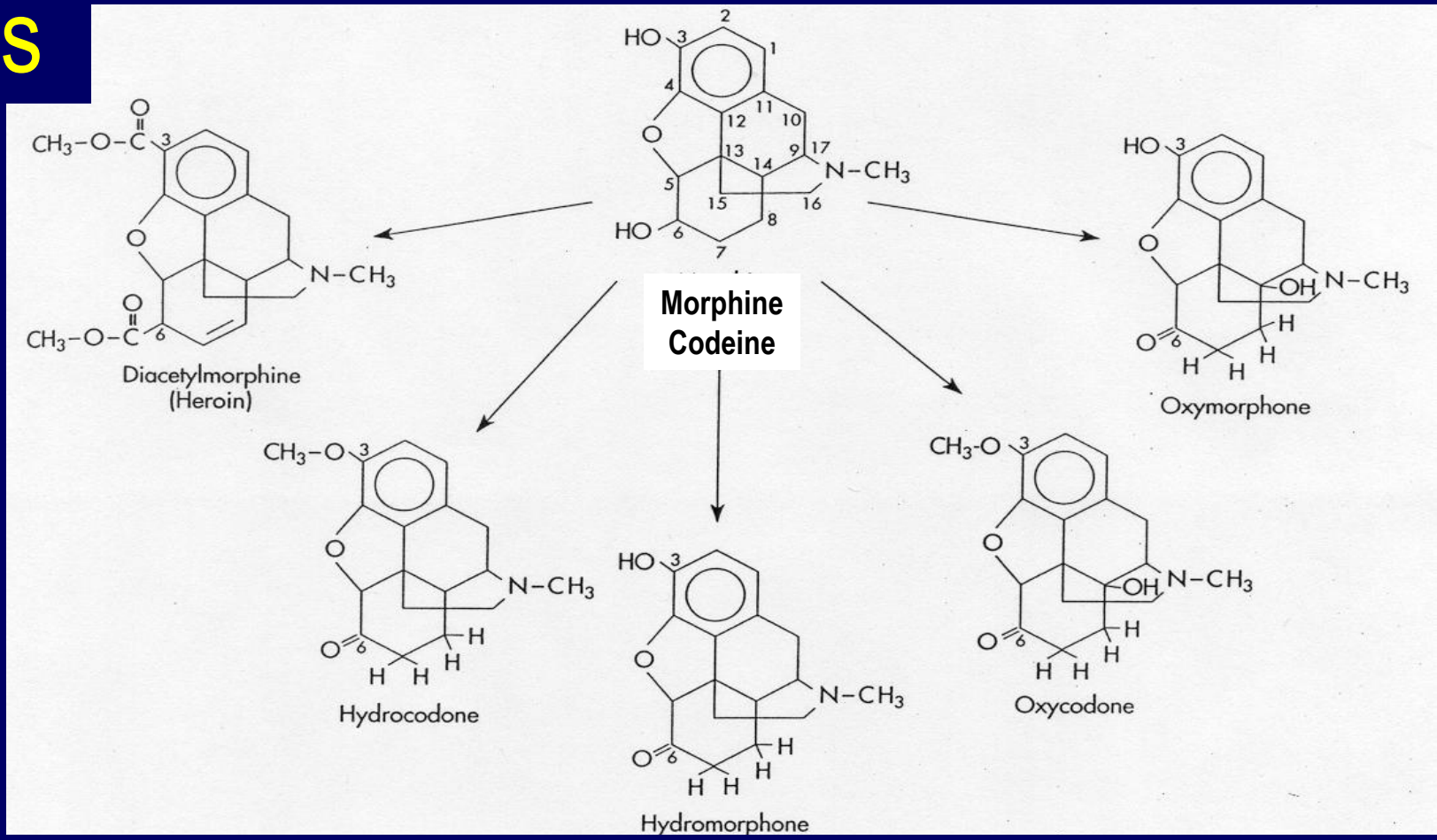
All of the following are possible explanations for her <u>opiate positive</u> drug test <u>EXCEPT</u>?

1. Illicit opioid (heroin) use during hospitalization
2. Heroin use prior to admission
3. Hydromorphone (Dilaudid) given for pain last night
4. Methadone given during hospitalization



Opioids

Natural & Semisynthetic



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

Case continued

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

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

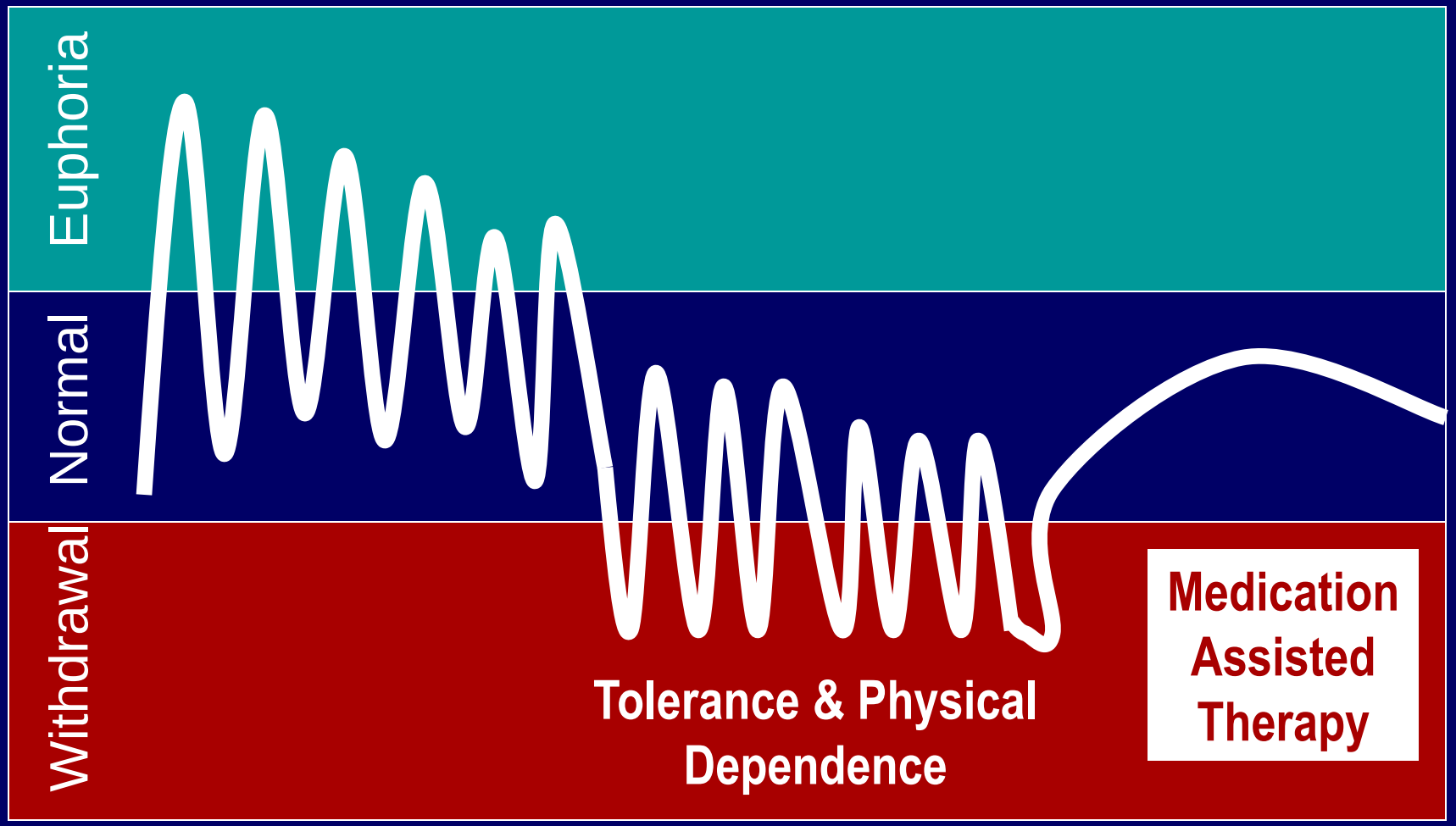
Reasons for Relapse

- 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

Medication Assisted Recovery

- Goals
  - Alleviate physical withdrawal
  - Opioid blockade
  - Alleviate drug craving
  - Normalized deranged brain changes and physiology
- Some options
  - **Naltrexone** (opioid antagonist)
  - **Methadone** (full opioid agonist)
  - **Buprenorphine** (partial opioid agonist)

Medication Assisted Therapy



Naltrexone

- Pure opioid antagonist
- Oral naltrexone
  - Well tolerated, safe
  - Duration of action 24-48 hours
  - FDA approved 1984
- Injectable naltrexone (Vivitrol®)
  - IM injection (w/ customized needle) once/month
  - FDA approved 2010
  - Patients must be opioid free for a minimum of 7-10 days before treatment

Oral Naltrexone

- 10 RCTs ~700 participants to naltrexone alone or with psychosocial therapy compared with psychosocial therapy alone or placebo
  - No clear benefit in treatment retention or relapse at follow up
- Benefit in highly motivated patients
  - Impaired physicians > 80% abstinence at 18 months

Cochrane Database of Systematic Reviews 2006

Injectable Naltrexone (XR-NTX)

- Multicenter (13 sites in Russia-OAT unavailable) DB RPCT 24 weeks
- 250 individuals with opioid dependence randomized to XR-NRT vs placebo
- All offered biweekly individual drug counseling
- Funded by pharmaceutical company - Alkermes

	XR-NTX (n=126)	Placebo (n=124)
Primary endpoint		
Proportion of weeks of confirmed abstinence	90·0% (69·9 to 92·4)	35·0% (11·4 to 63·8)
Patients with total confirmed abstinence	45 (35·7%, 27·4 to 44·1)	28 (22·6%, 15·2 to 29·9)
Secondary endpoint		
Proportion of self-reported opioid-free days over 24 weeks	99·2% (89·1 to 99·4)	60·4% (46·2 to 94·0)
Craving: mean change in VAS score from baseline	−10·1 (−12·3 to −7·8)	0·7 (−3·1 to 4·4)
Number of days of retention	>168‡	96 (63 to 165)

Krupitsky E, et al. Lancet, 2011

Methadone Hydrochloride

- Full opioid agonist
- 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”

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,[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 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 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

CRIT 2012

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 for full text of the original *JAMA* article.

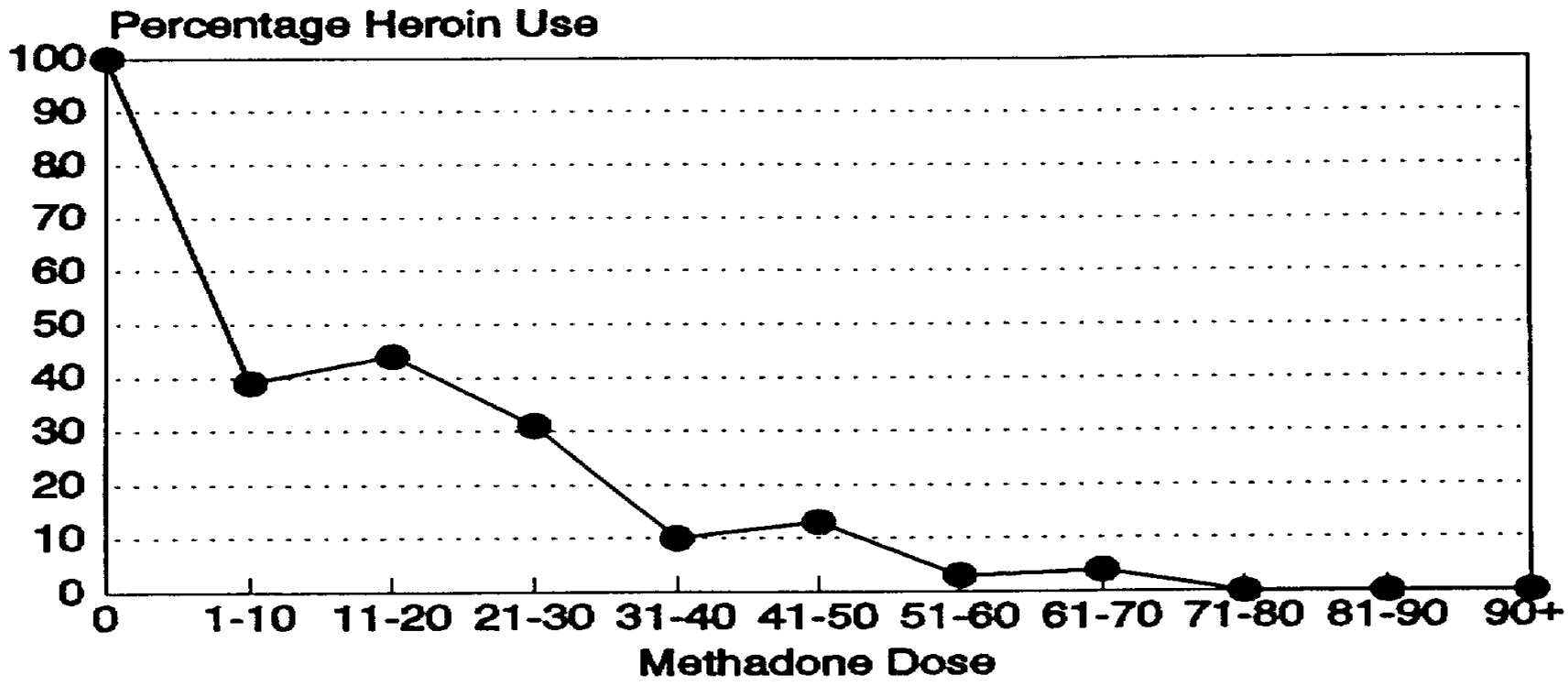
Commentary by Herbert D. Kleber, MD

Heroin became the street narcotic of choice. During World

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.

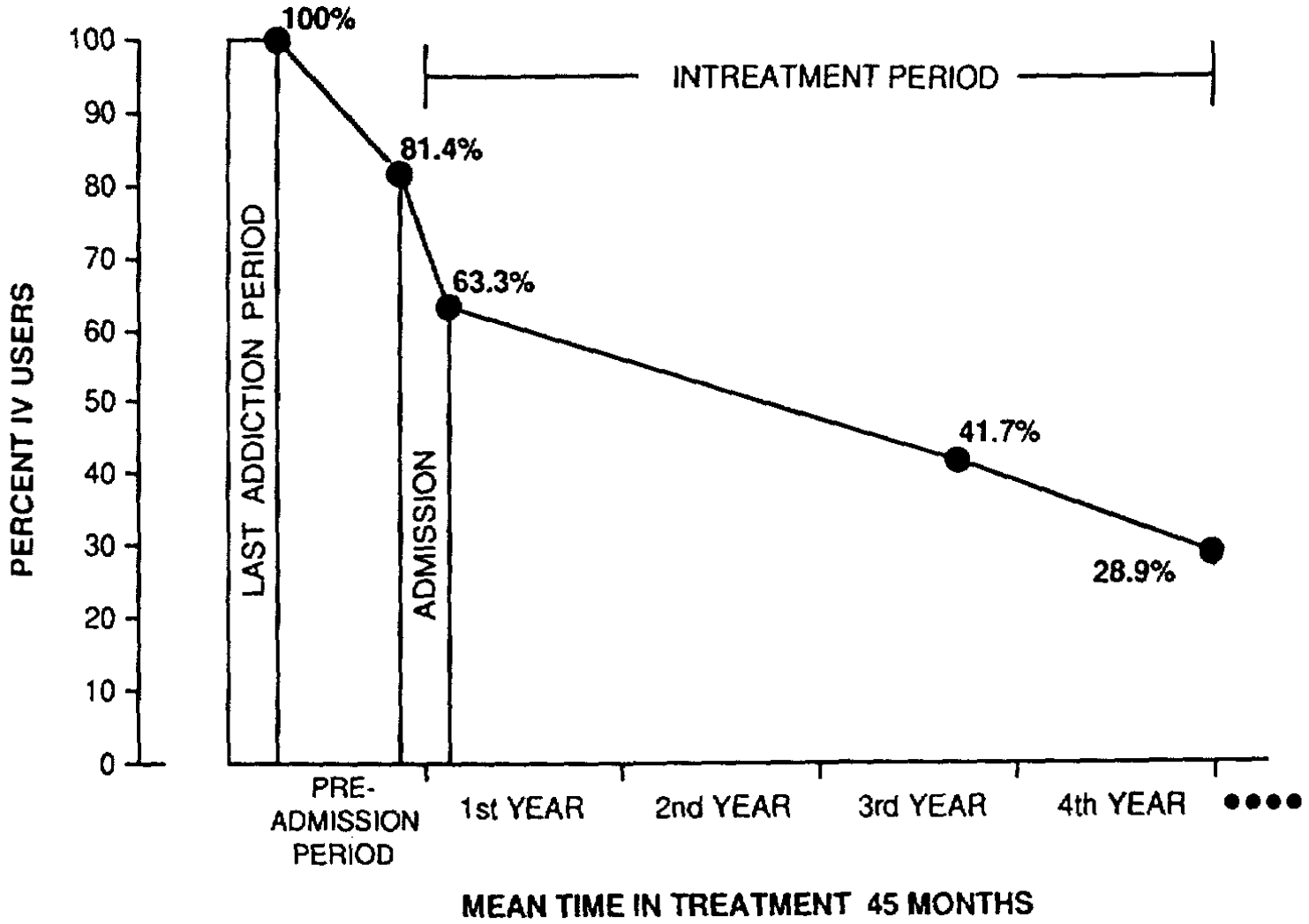
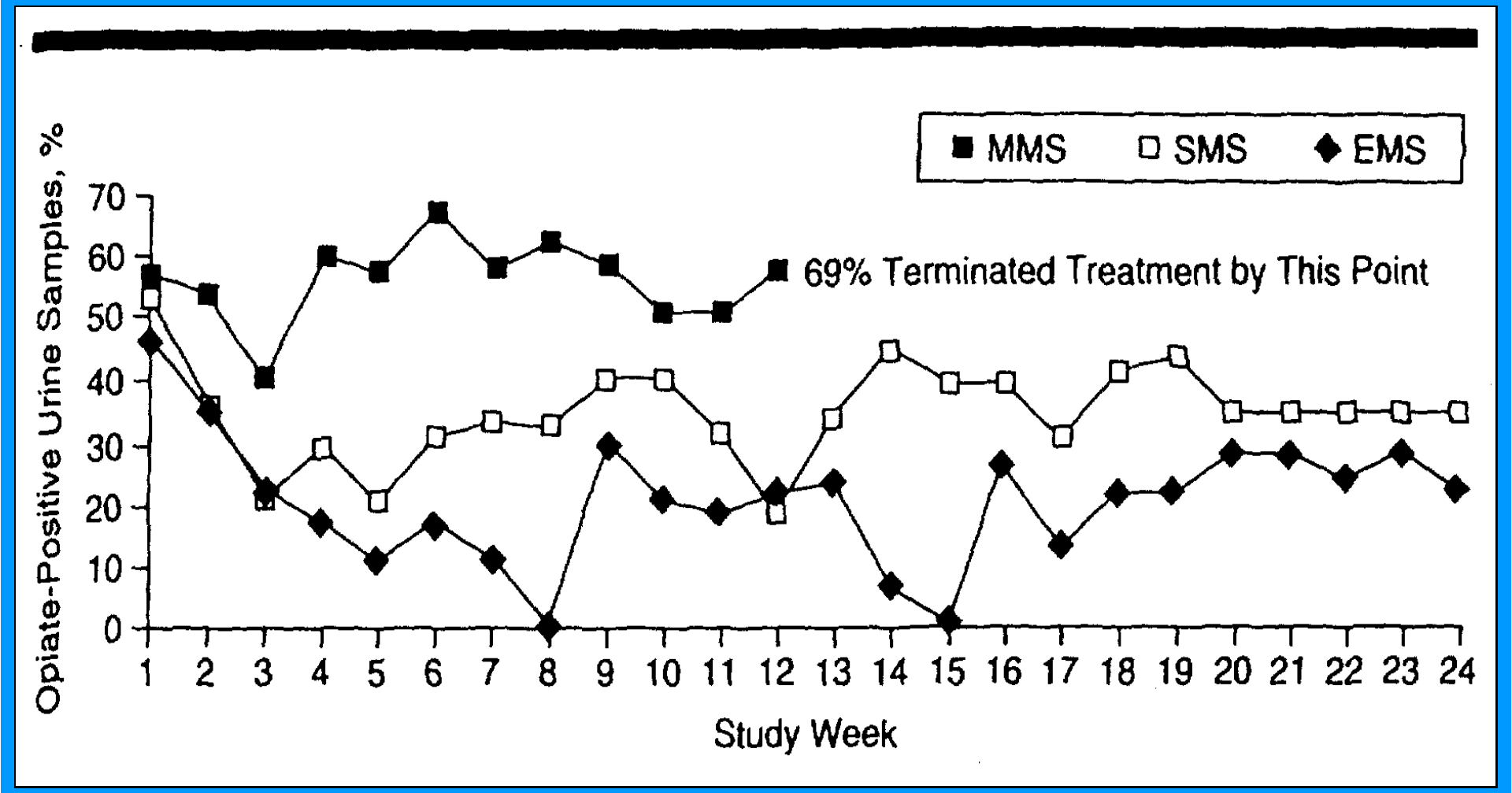


FIGURE 7.1. Impact of methadone maintenance treatment on intravenous drug use for 388 male methadone patients in six programs.

Ball JC, Ross A. The effectiveness of methadone maintenance treatment, 1991

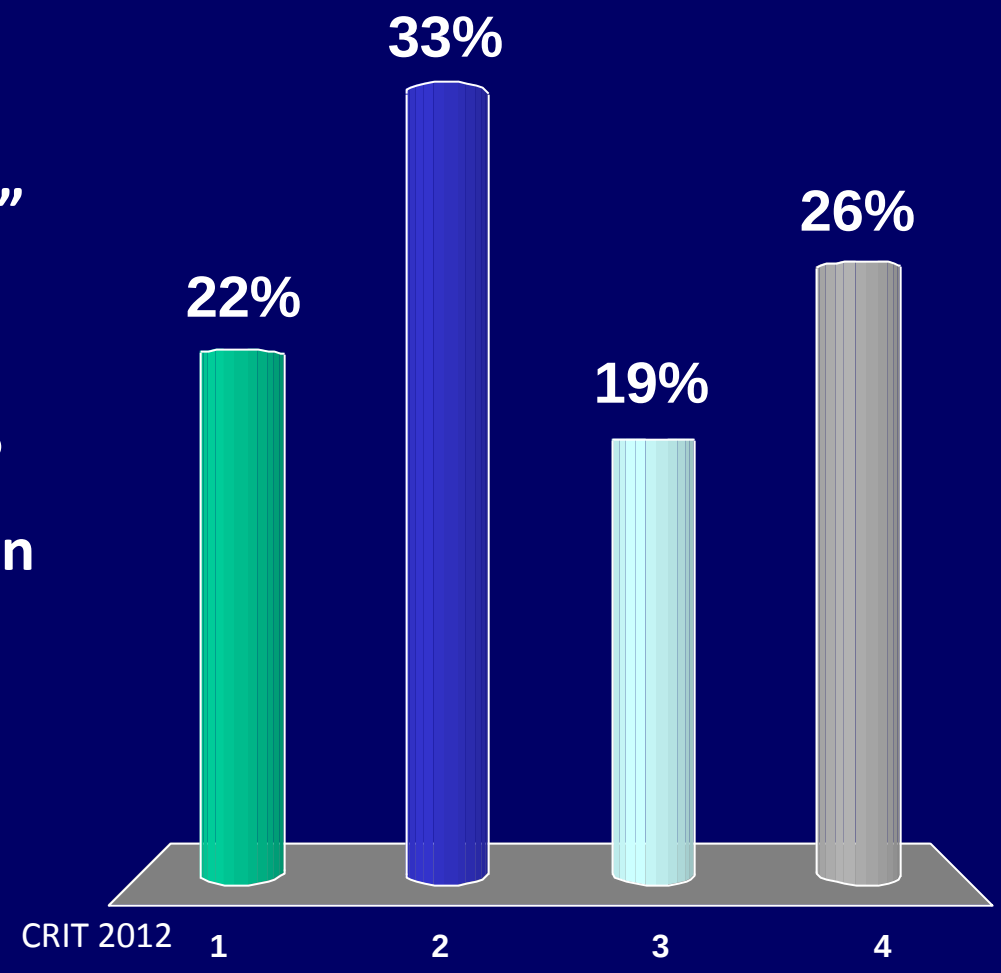
Effects of Psychosocial Services



McLellan, AT et.al , J AMA 1993

What is the single best question to assess a patient's success on methadone maintenance treatment?

1. Are you using drugs?
2. Are you on "take home" doses?
3. Are you compliant with methadone treatment?
4. How long have you been on methadone treatment?



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

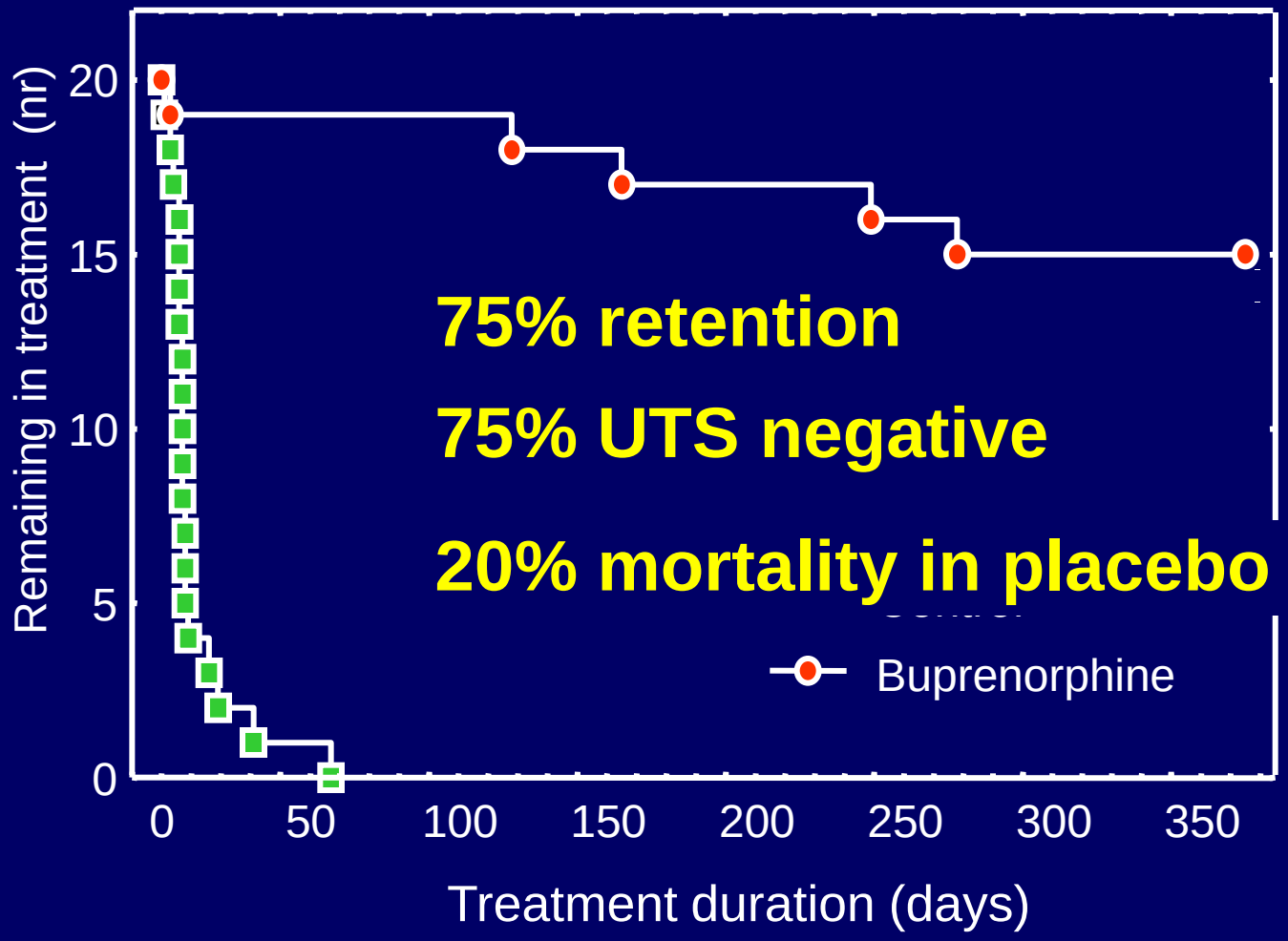
The physician is licensed under State law and "qualified" based on one of the following:

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

Buprenorphine

- Buprenorphine (Subutex or generic) "mono"
- Buprenorphine + naloxone (Suboxone)"combo"
  - Schedule III
  - Sublingual tablets, film
  - Treatment of opioid dependence
  - High receptor affinity
  - Slow dissociation
  - Ceiling effect for respiratory depression

Buprenorphine Maintenance vs Detox



Kakko J et al. Lancet 2003

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