Opioids
Research to Practice

CRIT Program
May 2008

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

Euphoria

Normal

Withdrawal

Tolerance and Physical Dependence

Acute use

Chronic use
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
- Needles from diabetic friend, no sharing
- 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

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

**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
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)
Heroin versus Methadone
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
  - IV Vancomycin
- Opioid withdrawal
  - Day 1 Methadone 20 mg
  - Day 2
    - Very anxious, demanded increase in methadone dose
    - She was off the floor for 2 hours
    - Medical team & nursing staff suspicious of illicit opioid use
    - Repeat urine toxicology screen was positive for “opiates”

How do you interpret this toxicology 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) and 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)
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
  - Referral
    - Detoxification program
    - Needle exchange
    - Acupuncture
    - Outpatient counseling
    - Methadone maintenance
Case continued

- **Recommended Options**
  - Narcotics Anonymous (NA)
  - Clonidine + NSAID + benzodiazepine + ...
  - Naltrexone
  - Buprenorphine maintenance
- **Referral**
  - Detoxification program
  - Needle exchange
  - Acupuncture
  - Outpatient counseling
  - Methadone maintenance
Opioid Detoxification Outcomes

- Low rate of retention in treatment
- Low rate of achieving abstinence
- Low rates of success in maintaining abstinence
  - < 50% at 6 months
  - < 80% at 12 months
Chronic Opioid Withdrawal

- Lasts months to years
- Secondary to derangement of endogenous opioid receptor system
- Symptoms
  - generalized malaise, fatigue
  - poor tolerance to stress and pain
  - craving for opioids
  - restlessness, insomnia
Maintenance Medication Goals

- Alleviate physical withdrawal \( (\text{low doses}) \)
- “Narcotic blockade” \( (\text{higher doses}) \)
- Alleviate drug craving \( (\text{higher doses}) \)
- Normalized deranged brain changes
- Normalized deranged physiology
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.

JAMA 1965
Figure 1 - Heroin Use in Past 30 Days
407 MM Patients by Current Methadone Dose

* Adapted from a study of 407 methadone maintenance patients.
Safety of Methadone Maintenance

• Prospective study of 129 patients
• Retrospective study of 1435 patients
• Greater than 3 years of treatment

• Results
  – No change in baseline LFTs
  – Normal hematologic and endocrinologic studies
  – 48% increased sweating
  – 22% decreased libido
  – 17% constipation

Effects of Psychosocial Services

McLellan, AT et.al, JAMA 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 ⇒ “Take homes”
What is the **one** most useful question to determine a patient's compliance with methadone maintenance treatment (i.e., negative urine toxicology screens, counseling, dosing, medical appointments, etc.)?

**Are you on take homes?**
If not, why not?

Please communicate with the methadone maintenance treatment program
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 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 done treatment, the approach to treating drug addiction has always struggled for acceptance, the forces of public opinion. “There is a stigma attached to addiction, addicts, and—sadly providers,” said Kreek, a supporter of the methadone maintenance approach to treating drug addiction.

Methadone maintenance has been a controversial issue in the United States, with some physicians acting as opioids to treat individuals with opioid addiction.

The Drug Enforcement Administration, in fact, considered methadone treatment illegal and had threatened to arrest Dole prior to the 1965 publication of the US government’s political courage,” said Jeroen, who became the first national...
Figure 8.1. Relapse to intravenous drug use after methadone maintenance treatment for 105 male patients who left treatment.
How long should methadone maintenance treatment last?

Long enough.
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
Medication Assisted Treatment Milestones

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:

![BuprenorphineCME.com]
Opioid Potency

% Efficacy
Opioid effect, sedation, respiratory depression

Log Dose of Opioid

Full Agonist
(Heroin, Oxycodone, Methadone)

Full Antagonist
(Naltrexone, Naloxone)
Buprenorphine: Ceiling Effect

- **Full Agonist**: Methadone
- **Partial Agonist**: Buprenorphine
- **Full Antagonist**: Naltrexone

**Efficacy**
- Opioid effect, sedation, respiratory depression

**Log Dose of Opioid**

- The graph shows the precipitated withdrawal effect of Buprenorphine compared to full agonists and full antagonists.
Effects of Buprenorphine Dose on *mu* Receptor Availability

MRI

Bup 00 mg

Binding Potential (Bmax/Kd)

0 -

4 -
Effects of Buprenorphine Dose on mu Receptor Availability

Slide Courtesy of Laura McNicholas, MD, PhD
Subutex® ("mono") & Suboxone® ("combo")
- Schedule III
- Sublingual tablets
- Treatment of opioid dependence
- "Combo"
  - Buprenorphine 2mg/naloxone 0.5mg
  - Buprenorphine 8mg/naloxone 2mg
- "Mono"
  - Buprenorphine 2 mg and 8 mg
- Maintenance dose = 8-32 mg ($8-12) per day
Buprenorphine Efficacy

- Studies (RCT) show buprenorphine more effective than placebo and equally effective to moderate doses 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
Buprenorphine Efficacy

75% retention
75% UTS negative
20% mortality in placebo group

Buprenorphine Efficacy

Proportion of treatment successes

>80% success rates

Duration of treatment (days)

Buprenorphine Summary

- Retention rates & efficacy comparable to methadone (80mg)
- “Ceiling” on opioid effects therefore low overdose risk
- Narcotic blockade
  - High affinity for opioid receptor
  - Slow dissociation from opioid receptor
- Abuse unlikely due to formulation w/ naloxone
  - Naloxone blocks opiate effect if injected
  - Naloxone is degraded (inert) if taking orally
Summary

• Heroin overdose is common in experienced users
• High risk period when tolerance is low
• Treat acute withdrawal inpatient with methadone 20-40mg to facilitate full medical/surgical treatment
• Refer for long-term substance abuse treatment
• Methadone maintenance, highly structured, with many years of proven efficacy, but w/ limitations
• Buprenorphine maintenance, less structured, effective as moderate dose methadone w/ fewer limitations