Opioids
Research to Practice

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Case

• 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 Use Disorder

Euphoria

Normal

Withdrawal

Tolerance & Physical Dependence

Acute use

Chronic use
Conflicting
Priorities...

TO NURSE IN CHARGE,

NORMAN IS OR HAVE TO LEAVE THE HOSPITAL GODS MONITOR I PROMISE YOU I WILL RETURN AT DINNER TIME, I JUST HAVE TO GET ME SOME HEROIN.

P.S.

SORRY THAT I LEFT BUT I KNOW YOU WOULD HAVE NOT LET ME GO SEE YOU AT DINNER TIME PROMISE.

5:30pm. No answer.
Substance abuse history

- \( \frac{1}{2} \) 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

### 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)

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

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**

- Morphine
- Codeine
- Diacetylmorphine (Heroin)
- Hydromorphone
- Hydromorphone
- Hydrocodone
- Oxycodone
- Oxymorphone

**Synthetic**

- Methadone
- Meperidine
- Fentanyl
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)
- Overdose prevention education and Intranasal Narcan
- 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**
Pharmacotherapy
Medication-Assisted Therapy (MAT)

• 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)

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Medication-Assisted Therapies — Tackling the Opioid-Overdose Epidemic

The rate of death from overdoses of prescription opioids in the United States more than quadrupled between 1999 and 2010 (see graph), far exceeding the combined death toll from cocaine and heroin overdoses. In 2010 alone, prescription opioids were involved in 16,651 overdose deaths, whereas heroin was implicated in 3036. Some 82% of the deaths due to prescription opioids and 92% of those due to heroin were classified as unintentional, with the remainder being attributed predominantly to suicide or “undetermined intent.”

Rates of emergency department visits and substance-abuse treatment admissions related to prescription opioids have also increased markedly. In 2007, prescription-opioid abuse cost insurers an estimated $2.5 billion — a substantial increase over previous years. These health and economic costs are similar to those associated with other chronic diseases such as asthma and HIV infection.

These alarming trends led the Department of Health and Human Services (HHS) to deem prescription-opioid overdose deaths an epidemic and prompted multiple federal, state, and local actions. The HHS efforts aim to simultaneously reduce opioid abuse and safeguard legitimate and appropriate access to these medications. HHS agencies are implementing a coordinated, comprehensive efforts addressing the key risks involved in prescription drug abuse, particularly opioid-related overdoses and deaths.
Medication-Assisted Therapy

Withdrawal

Euphoria

Normal

Tolerance & Physical Dependence

Acute use

Chronic use

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

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, “opioid blockade”
Methadone Maintenance
Over 45 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.

Enough review of evidence available in 1957, 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

Methadone Treatment Marks 40 Years

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 treatment, the approach always struggled for acceptance by the forces of public opinion. “There is a stigma against addicts, and—sadly—providers,” said Kreek, a long-time supporter of the methadone program.

“THE FARM”

Methadone maintenance, in fact, considered Dole’s illegal and had threatened to jail him prior to the 1965 publication of his findings. “I defy the US government with political courage,” said Jerome, who became the first national

JAMA 1965

JAMA 2005
Methadone Maintenance
Still controversial...
Methadone Maintenance Dosing

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

Percentage Heroin Use

Methadone Dose

* 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.
Effects of Psychosocial Services

McLellan, AT et.al., JAMA 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 drug testing
- Psychiatric services
- Medical services
- Methadone dosing
  - Observed daily ⇒ “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
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 versus Taper

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

Buprenorphine Efficacy

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

Johnson et al. NEJM 2000
Fudala PJ et al. NEJM 2003
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.