PSYCHIATRY'S ROLE IN TACKLING THE OPIOID CRISIS: HOW TO OPTIMIZE MEDICATION-ASSISTED TREATMENT
Learning Objectives

• Distinguish between the treatment options for opioid use disorder in terms of their mechanisms and clinical profiles

• Optimize strategies to reduce adverse effects during medically-supervised withdrawal

• Apply maintenance strategies for opioid use disorder that minimize the risk of relapse
Epidemic: Prescribing Opiates for Pain

- Opiate prescriptions: 76 million in 1991 to 207 million in 2013
- 15.3 million opiate prescriptions in 2013 for Medicare patients
- 2 million Americans addicted to prescription opiates, annually
- Physicians blamed for opiate addiction “as much as public holds individuals responsible for abusing the medications”
- FDA: “should forbid marketing opiates for chronic pain”
- CDC: limits opiates to 7 days of treatment for short-term pain
- Chronic opiates *amplify pain* through tolerance, hyperalgesia, and inflammation
- **Fentanyl** is the new threat of overdose & death because current addiction treatments do not block this class of opiate analgesics
Pattern of Opioid Addiction

Profounding craving

Profounding dysphoria and physical and emotional pain

Compulsivity

Anticipation/preoccupation

Tolerance to intoxication

Abstinence

Binge/intoxication

**DSM-5 Criteria for Diagnosis of Opioid Use Disorder (OUD)**

At least two criteria must be met within a 12-month period

1. Take more/longer than intended
2. Desire/unsuccessful efforts to quit opioid use
3. A great deal of time taken by activities involved in use
4. Craving, or a strong desire to use opioids
5. Recurrent opioid use resulting in failure to fulfill major role obligations
6. Continued use despite having persistent social problems
7. Important activities are given up because of use
8. Recurrent opioid use in situations in which it is physically hazardous (e.g., driving)
9. Use despite knowledge of problems

**10. Tolerance**

**11. Withdrawal**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Mild:</td>
<td>2-3 symptoms</td>
</tr>
<tr>
<td>Moderate:</td>
<td>4-5 symptoms</td>
</tr>
<tr>
<td>Severe:</td>
<td>6 or more symptoms</td>
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</tbody>
</table>

Known Risk Factors for Opioid Misuse

- Age ≤45 years
- Psychiatric disorder
- Substance use disorder
- History of:
  - Legal problems
  - Motor vehicle accidents
  - Preadolescent sexual abuse (in women)
- Family history of:
  - Substance use disorder
- Poor support

Recent Annual US Prevalence of Opioid-Related Behavior

In one year…

- **11.5 million** people in the US used opioid pills in a manner that was not as prescribed
- **2.6 million** people in the US were addicted to opioid pills or heroin
- **62.3 million** people in the US filled at least one prescription for opioids
  - 20.7% reported having shared pills
  - estimated **3.27%** become iatrogenically addicted

Rates of iatrogenic addiction can be drastically lower than 3.27% if clinicians attend to patients’ histories.

For pain patients with no history of alcohol or drug problems, the rate is only 0.19%.

This knowledge is now reflected in guidelines for prescription, and the annual number of prescriptions written in the US has decreased by 16% since peaking in 2012.

Drug overdose deaths in the United States involving specific drugs and drug classes from 2012 to 2016.

- Heroin: 9,580 deaths
- Natural & semi-synthetic opioids: 12,000 deaths
- Synthetic opioids*: 19,413 deaths
- Methadone: 4,000 deaths

*excluding methadone

Endogenous Opiate Neurotransmitters
The Opioid System

- Nucleus accumbens
- Dopamine
- GABA
- Endogenous opioid
- VTA
- DA neuron
- GABA interneuron
Agonist Actions at Mu Opioid Receptors

Endogenous Opioid

Heroin

Prescription Opioids
Norepinephrine and Side Effects
Medication-Assisted Treatment (MAT)

- Methadone
- Buprenorphine
- Naltrexone
Methadone

- First approved MAT for opioid use disorder
- Full agonist at mu opioid receptors
- Does not elicit the same euphoric high experienced after using heroin or Rx opioids
- Allows individuals with opioid use disorder to discontinue use of heroin without experiencing the withdrawal symptoms
- Only available through specialty clinics
  - Patient must make daily visits
  - Restriction to access
  - Stigma
- Increased risk for respiratory depression
- Available in both liquid and tablet formulation

Buprenorphine

- Partial agonist at mu opioid receptors
  - Acts as an antagonist in the presence of a mu opioid receptor agonist, blocking its effects
- May precipitate active withdrawal symptoms in individuals currently using heroin or Rx opioids
- Patients should be experiencing at least some mild withdrawal before initiating buprenorphine
- Does not need to be administered at specialty clinics (although specialty licensing for the prescriber is required)
- Less risk for respiratory depression compared to methadone
- Available as a sublingual tablet and a film as well as a long-acting implant

Maintenance Using Buprenorphine: Efficacy

• Numerous outpatient clinical trials comparing efficacy of buprenorphine to placebo and to methadone
• Expect average daily dose to be somewhere between 8/2 and 24/6 mg of buprenorphine/naloxone
• Depot buprenorphine—lasts a month; full-dose range
  • Equivalent efficacy to sublingual film; enhanced compliance
• These studies conclude that:
  • Buprenorphine is more effective than placebo
  • Buprenorphine is as effective as moderate doses of methadone (e.g., 60 mg/day)

Buprenorphine Implant

• FDA approved for maintenance treatment of opioid dependence

• Patients should:
  • **Be stable** on ≤8 mg transmucosal buprenorphine for ≥3 months without need for supplemental dosing or adjustment
  • **NOT** have dose reduced for the purpose of transitioning
  • **NOT** be prescribed as-needed transmucosal buprenorphine

• Four implants are inserted subdermally and are removed by the end of the 6th month

• Examine insertion site after 1 week for signs of infection

• After one insertion in each arm, transition back to transmucosal
Methadone and Buprenorphine Efficacy

• More effective than placebo
• Efficacy of the medication is related to the dose
• Controlled studies have tested doses as high as 100 mg/day methadone and 16 mg/day buprenorphine
• Good treatment retention
• Decreased illicit opiate use (urines, self-reports)
• Improvements in other areas included increased employment, decreased criminal activity, and psychological adjustment (depression)

Buprenorphine-Naloxone Combination

- Naloxone is a mu opioid receptor antagonist that can block the actions of mu opioid receptor agonists or partial agonists.
- Buprenorphine-naloxone combination
  - Prevents diversion of buprenorphine
  - Taken sublingually, naloxone has little effect = no withdrawal
  - Diverted into inhaled or injected form, naloxone actions dominate = withdrawal
Opiate Abuse + Pain: Buprenorphine

- Advantages of buprenorphine + naloxone compared to other opiates
  - Medical safety – overdose prevented
  - Diversion very unlikely – precipitated withdrawal
  - Readily discontinued – mild withdrawal
  - Does not cause hyperalgesia – sustained pain relief
  - Prevents “doctor shopping” – blocks other opiates
  - Divided daily dosing for pain – 2 mg SL 4 × daily

Discontinuing Opioids or MAT

Withdrawal Severity

Heroin or Rx Opioids

Methadone

Buprenorphine

Days since opiate
Drug Interactions With Buprenorphine

• Few clinically significant interactions compared with methadone

• Benzodiazepines, or sedating drugs in combination with buprenorphine, can lead to overdose

• Medications metabolized by cytochrome P450 3A4

• Methadone also interferes with 2D6 metabolism

• Opiate antagonists: few effects

• Opiate agonists: mostly blocked; fentanyl

Naltrexone

- Mu opioid receptor antagonist
  - Binding of naltrexone to mu opioid receptors results in no effect yet blocks the actions of opioid agonists
- Individual should be free of opioid agonists for 7-10 days before initiating naltrexone
  - May precipitate withdrawal in those actively using opioids
- Does not require specialty facilities or licenses
- Relatively little risk of respiratory depression or overdose
- Available as both oral and 30-day depot formulations

What Happens If an Individual on Naltrexone Uses Heroin (or Rx Opioids)?

- Euphoric effects
- Reinforcement

- No euphoric effects
- Extinction learning

Relapse to heroin/Rx opioid use while on naltrexone may actually HELP with abstinence.
Naltrexone’s Pharmacokinetic Profile

Plasma Concentration: 50 mg (PO), 0–24 Hours

Fluctuations each month

Depot Naltrexone

Provide sustained naltrexone release following injection

- Avoid daily loss of therapeutic plasma levels, maintaining levels for 30 days
- Eliminate need for daily dosing by patient
- Reduce repetitive high plasma peaks
- Eliminate first pass metabolism

Depot Naltrexone Pharmacokinetics

Oral vs. Depot Naltrexone: Opiates

• Retention and urine results compared between oral (n = 69) and long-acting injectable naltrexone (n = 42); retention in treatment and opiate use in the first 8 weeks post-detoxification were compared
• Long-acting injectable naltrexone produced significantly better outcome than oral naltrexone on days retained in treatment and proportion of opiate-free urines
  • Days retained: depot 42 vs. oral 32
  • Opiate-free urines: depot 0.52 vs. oral 0.37

Depot Naltrexone: Study Design and Outcomes

- Randomized, placebo-controlled 6-month outpatient clinical trial in 250 opiate-addicted patients
- Assigned to depot naltrexone vs. placebo after 7 days opiate-free while at inpatient setting
- Dose of about 25 mg daily from monthly injection
- 6-month outcome
  - 1.6 × more abstain completely on depot naltrexone: 36% vs. 23%
  - Average depot naltrexone patients attain 90% opiate-free weeks vs. average placebo patients attain 40% opiate-free weeks

Sustained Complete Abstinence With Depot Naltrexone

Abstinence: opiate-free from weeks 5–24

![Graph showing the comparison between Placebo (n = 124) and Naltrexone (n = 126) with percentages of patients abstinent.]

- Placebo: 23% (n = 124)
- Naltrexone: 36% (n = 126)

$P = .0002$
Adverse Events: Depot Naltrexone

Depot naltrexone was well tolerated in opiate-dependent patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Depot naltrexone n = 126</th>
<th>Placebo n = 124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase increased</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Influenza</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Toothache</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Depot Naltrexone:
Rare Severe Adverse Events

- Precipitated withdrawal, if not detoxed
- Injection site reactions (mild mostly)
  - Sterile abscess from injection into fatty tissue
- Eosinophilic pneumonia (rare)
- Large increase in LFT (doses > 300 mg daily)

LFT = liver function test.

Effectiveness of Extended-Release Naltrexone vs. Buprenorphine-Naloxone for Opioid Relapse Prevention

- In a 12-week study from Norway, extended release injectable naltrexone was as safe and effective as buprenorphine-naloxone in maintaining short-term abstinence from illicit opioids\(^1\)

- In a 24-week, open-label, randomized controlled study in the US, buprenorphine-naloxone was superior to injectable naltrexone in preventing relapse in the entire population studied\(^2\)
  - However, more than \(\frac{1}{4}\) of participants dropped out of naltrexone treatment before it had even begun due to failure to get through detoxification and start treatment
  - When treatment was successfully initiated in the US study, both medications were comparably safe and effective in preventing relapses

Tips and Tricks for MAT
Mitigating Withdrawal Symptoms During Transition to MAT or Between MATs

**Autonomic Symptoms**
- α2 adrenergic agonists (e.g., lofexidine, clonidine)

**Anxiety/Restlessness**
- Benzodiazepines
- Antihistamines

**Insomnia**
- Sedating antidepressants (e.g., trazodone)
- Nonbenzodiazepine hypnotics (e.g., eszopiclone)
- Sedating atypical antipsychotics (e.g., quetiapine)

**Musculoskeletal pain**
- NSAIDs (e.g., ibuprofen)
- Aniline algesics (e.g., acetaminophen)
- Antispasmodics (e.g., cyclobenzaprine)

**GI Distress**
- Oral hydration
- Neuroleptic antiemetics (e.g., prochlorperazine)
- 5HT3 antagonists (e.g., ondansetron)
Opiate Detoxification: New Ways to Transition to Depot Naltrexone

- Needed to reduce tolerance and hyperalgesia
- Stops pro-inflammatory opiate effects
- Detox fails unless patient is transitioned to sustained antagonist or maintenance: buprenorphine

Innovative approaches:
- Clonidine or lofexidine
- Lofexidine/naltrexone – rapid
- Buprenorphine

The rapid naltrexone protocol is not FDA approved.
Clonidine vs. Lofexidine

- Both adrenergic antihypertensives
- Non-abusable, oral use
- Dose titration not needed with lofexidine
- Lasts 7 days (except methadone)
- Targets autonomic symptoms
- Anxiety; diarrhea not well relieved
- Side effects: sedation, orthostatic hypotension

• Lofexidine has been widely used in Europe for >20 years
• Recently FDA approved – effective as clonidine; fewer side effects, greater patient acceptance
• Fixed dosing from 2.4 mg to 3.2 mg daily
• Treatment strategy very similar to clonidine
• Can use rapid detoxification variations with naltrexone

Severity of Withdrawal After Methadone Discontinuation

Days since last methadone dose

Severity of Withdrawal

Abrupt discontinuation

With lofexidene + naltrexone

With lofexidene
Severity of Withdrawal
After Buprenorphine Discontinuation

Days since last buprenorphine dose

Abrupt discontinuation

With lofexidine + naltrexone

With lofexidine

Overdoses Now From Fentanyl: Need for Anti-fentanyl Vaccination

• Methadone, naltrexone, or buprenorphine do **not** block fentanyl overdoses or “high”

• A vaccine against fentanyl is effective in animals, and needs to move into humans
Summary

• Opioid use disorder (OUD; including heroin and prescription opioids) is an epidemic we are currently faced with

• Medication-assisted treatment (including methadone, buprenorphine, and naltrexone) may be our best option in treating OUD

• The 3 MATs have differing mechanisms of action with varying effects on the opioid system

• There are several strategies for transitioning patients from opioid use to MAT and from one MAT to another

• Mitigating withdrawal symptoms using MAT and non-opioid therapies may provide patients with OUD the best opportunity for maintained abstinence and recovery
Francine is a 42-year-old patient addicted to oxycodone. She has recently begun treatment with naltrexone. At mu opioid receptors, naltrexone acts as a/an:

1. Agonist
2. Partial agonist
3. Antagonist
Which of the following interact with mu opioid receptors as full agonists?

1. Endogenous opioids
2. Heroin
3. Rx opioids (e.g., oxycodone)
4. 1 and 2 only
5. 1 and 3 only
6. All of the above
Ivan is a 25-year-old with OUD. He is concerned that the heroin he is obtaining on the streets may be laced with fentanyl. Which of the following MATs is effective against fentanyl overdose?

1. Methadone
2. Buprenorphine
3. Naltrexone
4. All of the above
5. None of the above