MANAGING OPIOID WITHDRAWAL AND OPIOID USE DISORDER (OUD)

Michelle Meyer, PharmD, BCPS, BCNSP
Andrea Wetshtein, PharmD, BCPS, CPE
OhioHealth Grant Medical Center
OBJECTIVES

Pharmacist Learning Objectives

• Outline symptoms of opioid withdrawal and the expected timeframe these would occur
• List treatment options for opioid withdrawal
• Describe different options for medication assisted therapy (MAT)
• Design a treatment plan for acute pain in patients on MAT

Technician Learning Objectives:

• List treatment options for opioid withdrawal
• Describe common medications used to treat opioid use disorder
HEROIN USE

- Heroin related deaths have more than quadrupled since 2010
- Approximately 75% of heroin users abused prescription opioids prior to using heroin
- In 2015 Ohio lead the nation in fentanyl related deaths and was second only to California in opioid overdose deaths
OPIOID EPIDEMIC - OVERDOSE

Overdose Deaths Involving Opioids, by Type of Opioid, United States, 2000-2015

- Any Opioid
- Heroin
- Natural & Semi-Synthetic Opioids
- Other Synthetic Opioids (e.g., fentanyl, tramadol)
- Methadone

Each day, more than 1,000 people are treated in emergency departments for not using prescription opioids as directed.
CHANGING PRESCRIBING PATTERNS

Figure 7. Number of Opioid Doses* Dispensed to Ohio Patients 2011-2015

There were 81 million fewer doses of opioids dispensed to Ohio patients in 2015 compared to 2011.

Source: State of Ohio Board of Pharmacy, Ohio Automated Rx Reporting System.

*Does not include liquids
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PHASES OF OPIOID WITHDRAWAL

• Acute (initial)
  • Anxiety, dysphoria, insomnia, temperature instability
  • Evaluated with Clinical Opiate Withdrawal Scale (COWS)
  • Typically what is evaluated in the inpatient setting

• Chronic (protracted)
  • Anxiety, depression, anhedonia, and sleep disturbances
  • Research is limited
  • No consensus on the term or definition exists
## TIMING OF OPIOID WITHDRAWAL

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Half-Life</th>
<th>Onset of Withdrawal Symptoms After Exposure</th>
<th>Typical Duration of Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>2-6 min</td>
<td>6 h</td>
<td>8-10 days</td>
</tr>
<tr>
<td>Methadone</td>
<td>8-150 h (mean 35 h)</td>
<td>24-96 h</td>
<td>10-14 days</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>37 h</td>
<td>6-24 h</td>
<td>Milder withdrawal than other opioids; usually resolves within 7 days</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.5-7 h</td>
<td>8-12 h</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>3-5 h</td>
<td>6-12 h</td>
<td>7-14 days</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>7-9 h</td>
<td>8-12 h</td>
<td>5-14 days</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>11-36 h</td>
<td>3-5 h</td>
<td>4-5 days</td>
</tr>
</tbody>
</table>
# OPIOID WITHDRAWAL SYMPTOMS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Scores</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting Heart Rate</td>
<td>0-4</td>
<td>0 = 80 or less; 1= 81-100; 2= 101-120; 4= greater than 120</td>
</tr>
<tr>
<td>Sweating</td>
<td>0-4</td>
<td>0 = none; 4 sweat streaming from face</td>
</tr>
<tr>
<td>Restlessness</td>
<td>0-5</td>
<td>0 = sits still; 5= unable to sit still (even for a few seconds)</td>
</tr>
<tr>
<td>Pupil Size</td>
<td>0-5</td>
<td>0 = normal; 5 =dilated (only iris rim visible)</td>
</tr>
<tr>
<td>Bone or Joint Aches</td>
<td>0-4</td>
<td>0 = none; 4 = severe discomfort</td>
</tr>
<tr>
<td>Runny nose or tearing</td>
<td>0-4</td>
<td>0 = none; 4 = constant</td>
</tr>
<tr>
<td>Gastrointestinal Upset</td>
<td>0-5</td>
<td>0 = none; 5 = multiple episodes of vomiting or diarrhea</td>
</tr>
<tr>
<td>Tremor</td>
<td>0-4</td>
<td>0 = none; 4 = gross tremor</td>
</tr>
<tr>
<td>Yawning</td>
<td>0-4</td>
<td>0 = none; 4 = yawning several times per minute</td>
</tr>
<tr>
<td>Anxiety and Irritability</td>
<td>0-4</td>
<td>0 = none; 4 = severe, precluding participation</td>
</tr>
<tr>
<td>Gooseflesh skin</td>
<td>0-5</td>
<td>0 = smooth; 5 = prominent piloerection</td>
</tr>
</tbody>
</table>

Score: 5-12 mild; 13-24 moderate; 25-26 = severe
Patients with concurrent pain (daily IV heroin user with abscess or opioid dependent patient s/p MVA)

- Short-acting opioids
  - Dosed for tolerance
  - May reach max doses before relief if using APAP containing

- Long-acting opioids
  - Scheduling opioids can ease tension between nursing and patient
  - Stable opioid levels

Use multi-modal analgesia in treatment plans

Under treatment of pain in opioid use disorder patients increases incidence of relapse.
OPIOID REPLACEMENT THERAPY

Patients without pain

- Frequently morphine or methadone in neonatal abstinence syndrome-Finnegan Score
- COWS scores rating as moderate to severe
- Usually using methadone or buprenorphine products in adults
- Legally can treat inpatients as long as they are admitted for another medical reason
  - Title 21 Code of Federal Regulations. Section 1306.07 Administering or dispensing of narcotic drugs.
<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Alpha 2 agonist</th>
<th>Antihistamine</th>
<th>Anti-psychotic</th>
<th>Anti-emetic</th>
<th>Anti-diarrheal</th>
<th>Anti-cholinergic</th>
<th>Anti-depressant</th>
<th>Analgesic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commonly prescribed</td>
<td>clonidine</td>
<td>hydroxyzine</td>
<td>quetiapine</td>
<td>Ondansetron or prochlorperazine</td>
<td>loperamide</td>
<td>dicyclomine</td>
<td>trazodone</td>
<td>APAP or ibuprofen</td>
</tr>
<tr>
<td>Usual dosing</td>
<td>0.1-0.2mg Q6-8 hours</td>
<td>25mg Q4-6 hours</td>
<td>25mg QHS or TID</td>
<td>Ondan: 4mg Q6 hours Prochl: 5-10mg Q6 hours</td>
<td>2-4mg after each loose stool (max 16mg/day)</td>
<td>10-20mg Q6 hours</td>
<td>50-100mg QHS</td>
<td>650mg Q4 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>600-800mg Q6 hours</td>
</tr>
<tr>
<td>Symptom(s) treated</td>
<td>All autonomic symptoms (sweating, diarrhea, abdominal cramps, nausea, anxiety, and agitation)</td>
<td>Helps with anxiety and agitation through generalized sedation</td>
<td>Antagonist of multiple neuro-transmitters, skin crawling, sedation helps with agitation and insomnia</td>
<td>Nausea, if using a 1st generation anti-psychotic will also have some sedation which would treat anxiety and agitation</td>
<td>Diarrhea</td>
<td>Abdominal cramping, watery eyes, diarrhea</td>
<td>Insomnia, agitation</td>
<td>myalgias</td>
</tr>
</tbody>
</table>
GABAPENTIN FOR OPIOID WITHDRAWAL

- Doses of 900-1600mg/day studied
- Most benefit seen with symptom relief of feeling cold, yawning, muscle tension, diarrhea, and dysphoria
- May also help with kindling mechanism (worsening symptoms with repeated episodes)
- Also data supporting use in ETOH withdrawal
MEDICATION ASSISTED THERAPY (MAT)

- The use of medications in **COMBINATION** with counseling and behavioral therapies for the treatment of substance use disorders
- Three current medications approved for use as MAT
  1. Methadone
  2. Buprenorphine
  3. Naltrexone
· Brand names:
  · Dolophine, Methadose

· Class:
  · Full Mu agonist and NMDA antagonist

· Use:
  · To reduce cravings and withdrawal symptoms from opioids

· Dosage Forms:
  · PO Tablets
  · PO Solution
  · IV Solution
METHADONE

- Advantages:
  - Slows brain uptake and reduces euphoria in oral dosing
  - Beneficial in patients finding no response to other MAT medications

- Disadvantages:
  - Only available through outpatient treatment programs which MOST patients must visit daily

- Clinical Pearls:
  - Start at no more than 30 mg **total daily dose**
  - QTc prolonging agent—watch for drug interactions
  - Use with caution in patients with liver dysfunction
BUPRENORPHINE

- Brand Names:
  - Subutex, Suboxone, Zubsolv

- Class:
  - Partial Mu agonist

- Use:
  - To reduce cravings and withdrawal symptoms from opioids

- Dosage Forms:
  - Sublingual film
  - Sublingual tablet
  - Topical patch (for pain management only)
BUPRENORPHINE

- Advantages:
  - Wider availability than methadone, patients can take at home

- Disadvantages:
  - Plain buprenorphine product has high abuse potential
  - High $$$ to patients

- Clinical Pearls:
  - Use plain buprenorphine product in pregnant women
  - Takes up to 20 min for sublingual tablet to dissolve
  - Depot injection and continuous infusion pump recently FDA approved
MM is a 39 year old male who uses IV heroin daily. Admitted for treatment of staph bacteremia. He is obviously agitated, complaining of worsening withdrawal and is concerned he will have to leave AMA to resolve his symptoms.
PATIENT CASE #1

- Patient complains of multiple episodes of diarrhea and terrible abdominal cramping. On physical exam, he has a HR of 105, BP 130/72, Temp 99.4. He has some beads of sweat on his face and reports feeling chilled. His pupils are moderately dilated. You can see that he has a slight tremor when he holds out his hands, but whenfinished he returns to rocking back and forth in bed, rubbing his knees. You have not observed any yawning, but do note that his nose is running.
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PATIENT CASE #1

- The hospitalist approaches you about recommendations for treating opioid withdrawal for MM. She is agreeable to starting methadone, but she is unsure how to dose it. What methadone dose do you recommend for MM?
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PATIENT CASE #1

- Which non-opioid meds would be most appropriate adjuncts for treating MM’s symptoms of withdrawal?
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NALTREXONE

- Brand Names:
  - ReVia, Vivitrol

- Class:
  - Full Mu antagonist

- Use:
  - To diminish the reinforcing effects of opioids

- Dosage Forms:
  - PO tablets
  - Depot Injection
NALTREXONE

- Advantages:
  - Does not result in physical dependence
  - Non-sedating

- Disadvantages:
  - Poor patient compliance (with PO tabs)
  - Management of acute pain crisis can pose a challenge

- Clinical Pearls:
  - Initiation requires prolonged abstinence – 7 days
  - Must stop PO naltrexone 48 to 72H before surgery in order for opioids to be effective
  - Within the first 14 days of depot injection, unable to overcome the mu receptor blockade for pain control
AVAILABILITY OF MAT

- Methadone = clinic
  - Dosed in clinic
  - Take home bottles
  - Do not submit data to OARRS

- Buprenorphine = DATA2000 waiver (XDEA)
  - Can be filled in multiple day prescription
  - Dosing can be verified in OARRS

- Naltrexone
  - No prescriptive restrictions
  - Increasing court mandated use
  - May not show up on ESI as frequently given in the office setting
A PATIENT IS ADMITTED TO YOUR SERVICE ON MAT—NOW WHAT?

Strategies to manage acute pain crisis in patients on MAT
PATIENT CASE #2

- 57 y.o. male presented to your hospital for a TKA. He has a history of HTN, DM2 and substance use disorder. His SUD is currently being managed with buprenorphine-naloxone sublingual tablets 8-2mg SL twice daily. He is anxious about controlling his pain after surgery.

- What recommendations would you make to the surgery team in order to control this patient’s pain?
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APPROACHES TO PAIN CRISIS IN PATIENTS ON MAT

- General Considerations
  - Maximize non-opioid therapies
  - Patients on MAT typically require higher doses of opioids to compensate for tolerance and/or effect of their MAT therapy
  - Try to avoid morphine as it is undistinguishable from heroin on a UDS
  - Transition to oral opioids as soon as clinically appropriate
    - If patient has nausea consider utilizing sublingual opioids
  - Identify and avoid patients’ previous drug of abuse and avoid as this may aggravate their addiction disorder

ALWAYS include the patient on their pain crisis plan
Buprenorphine products are not required to be stopped prior to surgery

SL films have greater bioavailability than buccal tablets
- Monitor for over or under dosing when switching between products

Approaches for pain management for SL buprenorphine products:
1) Maintain outpatient dose of Buprenorphine
   OR Buprenorphine/Naloxone and split home regimen into divided doses given every 4 - 6 Hours +/- an opioid at a tolerant dose
   --OR--
2) Maintain outpatient dose schedule of Buprenorphine
   OR Buprenorphine/Naloxone +/- an opioid at a tolerant dose
   --OR--
3) Discontinue Buprenorphine/Naloxone and add an opioid at a tolerant dose
PAIN CRISIS: METHADONE

- Confirm home dose with methadone clinic

- Approaches to pain management with methadone:
  - Split home dose of methadone Q8H
    - Duration of analgesia of methadone is 6-8H
  --OR--
  - Continue home DAILY dose of methadone
  - May consider adding opioids at a tolerant dose for either approach

- **NOTE:** If patient is enrolled in a methadone clinic, they will have to provide evidence of continued administration of methadone during their hospitalization in able to remain enrolled in the outpatient program
PAIN CRISIS: ORAL NALTREXONE

- Stop/Suspend use of oral naltrexone
  - Recommend to stop 72 hours prior to any PLANNED procedures
- Add opioids at an opioid tolerant dose

Other Considerations:
- Regional anesthetic techniques
- Ketamine
  - Typically dosed @ 0.1mg/kg/hr

- **NOTE:** A 7-10 day opioid free period is recommended before naltrexone can be resumed
PAIN CRISIS: DEPOT NALTREXONE

- Determine when the last naltrexone injection was administered
  - 0 to 14 days
    - Maximize adjuvant therapies
    - Regional anesthetic techniques
    - Continuous ketamine infusion at 0.1mg/kg/hr
    - Opioids are ineffective during this time frame
  - 15 to 28 days:
    - All recommendations for 0-14 days +/- opioids at a tolerant dose

- **NOTE:** Coordination with naltrexone provider is key
KETAMINE CLINICAL PEARLS

- Mechanism of Action: NMDA antagonist
- Dosing for pain
  - 0.1-0.2 mg/kg/hour – test dose prior to starting infusion
    - OR -
  - 10 mg/hr and titrate to pain control
    - OR -
  - PO: 10 mg Q8H and titrate to response
- Cautions/Concerns
  - Elevated blood pressure
  - History of psychosis or psychiatric disorder
  - Severe head injury
38 yo female presents with fever, severe L arm pain secondary to multiple abscesses. Her abscesses are going to require I&D and she is concerned with her pain control and is extremely fearful of withdrawal. She has a history of OUD, but has been in remission for the past 2 years and is being managed by the local methadone clinic. Her current MAT is methadone 120 mg PO Qday. She usually will take acetaminophen as needed for any minor aches and pain. She requests not to be started on oxycodone, as she reports this was her drug of choice when she was using. The hospitalist requests pharmacy’s assistance with managing this patient’s pain.

What recommendations would you make to the hospitalist to control this patient’s pain?
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PATIENT CASE - NALTREXONE

- 43 yo male presents as a level 2 trauma after an MVC. He has multiple rib fractures, a sternal fracture, and a L humerus fracture. In the trauma bay he continuously rates his pain as 10/10 and has not responded to IV hydromorphone 2mg.

- A nurse finds a medication alert necklace which shows the patient is on naltrexone. He then reports that he recently received a dose of Depot Naltrexone 11 days ago

- What recommendations would you provide the trauma team for the management of this patient’s pain?
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REFERENCES

- Patients on MAT require opioid tolerant doses.

- Undertreating pain in patients with OUD increases risk for relapse.