Opioid Pharmacology and Dosing Management

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1 These individuals were involved in the planning of the original 2017 content
2 These individuals were involved in the 2021 review, update, and approved rerelease of this activity
Educational Objectives

At the conclusion of this activity participants should be able to:

• Describe opioid pharmacology, efficacy, and safety

• Explain how to start, continue, modify, and discontinue or taper opioid therapy
Case 1

• 52 yo man with chronic cervical radiculopathy, cervicalgia and HTN. He has been taking naproxen 500mg BID for 10 years since undergoing spinal surgery that was not effective.
• He does not have depression or history of substance use disorder.
• He has tried multiple medications including TCAs, gabapentin, pregabalin, lidocaine patches, acetaminophen, and duloxetine.
• He has tried steroid injections and botox with little improvement.
• He works full time and exercises 3 days a week. He stretches 5 times a week.
• He requests an opioid to help with pain that is not relieved by his NSAID. He is not currently taking an opioid.
OPIOID PHARMACOLOGY
Opioids

Natural (Opiates) and Semisynthetic

Synthetic

From prior PCSS-O presentation
Activation of µ-Opioid Receptors

- Turn on descending inhibitory systems
- Prevent ascending transmission of pain signal
- Inhibit terminals of C-fibers in the spinal cord
- Inhibit activation of peripheral nociceptors
- **Activate opioid receptors in midbrain (“reward pathway”)**
Opioid Choices with Examples

- **Full mu agonists**
  - Morphine, Oxycodone, Hydrocodone, Hydromorphone, Fentanyl, Methadone, Oxymorphone

- **Partial mu agonist**
  - Buprenorphine

- **Mixed agonist/antagonists**
  - Pentazocine

- **Dual mechanism**
  - Tramadol, Tapentadol
### Opioid Choice*

<table>
<thead>
<tr>
<th>Immediate Release/Short-acting (IR/SA)</th>
<th>Extended Release/Long-acting (ER/LA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Morphine</td>
<td>- Morphine</td>
</tr>
<tr>
<td>- Hydrocodone</td>
<td>- Hydrocodone</td>
</tr>
<tr>
<td>- Hydromorphone</td>
<td>- Hydromorphone</td>
</tr>
<tr>
<td>- Oxycodone</td>
<td>- Oxycodone</td>
</tr>
<tr>
<td>- Oxymorphone</td>
<td>- Oxymorphone</td>
</tr>
<tr>
<td>- Tramadol</td>
<td>- Tramadol</td>
</tr>
<tr>
<td>- Tapentadol</td>
<td>- Tapentadol</td>
</tr>
<tr>
<td>- Codeine</td>
<td>- Methadone</td>
</tr>
<tr>
<td></td>
<td>- Fentanyl transdermal</td>
</tr>
<tr>
<td></td>
<td>- Buprenorphine transdermal</td>
</tr>
</tbody>
</table>

*Product-specific information at:
- [http://dailymed.nlm.nih.gov/dailymed](http://dailymed.nlm.nih.gov/dailymed);
- pharmacy medication guide;
- [https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm](https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm)
Opioid Formulations and Routes

- **Immediate release (IR/SA)**
- **Extended release/ Long acting (ER/LA)**

- **Transdermal**
  - Fentanyl
  - Buprenorphine

- **Oral**

- **Sublingual**
  - Buprenorphine off-label use for pain
Opioid Choice

- Duration and onset of action
  - Short-acting opioids increase risk of opioid-withdrawal mediated pain
- Patient’s prior experience
  - μ-opioid receptor polymorphisms
  - Individual differences in pharmacokinetics & pharmacodynamics

Currently there are NO proven abuse resistant opioids or formulations

**Opioid Choice**

**IR/SA Opioids**
- No opioid tolerance/opioid naïve
- Intermittent or occasional pain
- Incident or breakthrough pain with ER/LA opioids

**ER/LA Opioids**
- Not for acute pain treatment
- Opioid tolerance exists
- Constant, severe, around-the-clock pain
- To stabilize pain relief when patient using multiple doses of IR/SA opioids
- MUST NOT be broken, chewed or crushed

**Always start low and go slow**
IR/SA vs. ER/LA Uncertainties

- Insufficient evidence to determine whether ER/LA opioids are more effective or safer than IR/SA opioids
- Debate whether bolus dosing (IR/SA) or continuous exposure (ER/LA) is more likely to result in tolerance, hyperalgesia or addiction

Choose options that best meet patient needs

Individualize Treatment

Opioid Pharmacology

- Ongoing exposure causes tolerance
  - Larger dose required to maintain original effects (analgesic and AE’s)
  - Inter-individual variability in development of tolerance
  - “There appears to be no limit to the development of tolerance, and with appropriate dose adjustments, patients can continue to obtain pain relief.” — Inturrisi C. Clin J Pain 2002;18:S3-13
  - No theoretical dose ceiling
Dose-response Relationship for Respiratory Depression

- **A**
  - Ventilation (L/min)
  - Fentanyl dose (μg/kg)
- **B**
  - Ventilation (L/min)
  - Buprenorphine dose (μg/kg)

Dahan A. Br J Anaesth 2005;94:825-34
SELECTED OPIOIDS WITH UNIQUE PROPERTIES
Transdermal Preparations

• Convenient dosing
• Slow peak onset (>24-72h)
• Delayed offset (serum t½ life >17-26h)
• Sustained release requires predictable blood flow and adequate subcutaneous fat
• Absorption increased with fever or broken skin
• Absorption decreased with edema
• Some with metal foil backing not compatible with MRI

Fentanyl
• Every 72 hours
• Dosages (mcg/hr): 12, 25, 37.5, 50, 62.5, 75, 87.5, 100

Buprenorphine
• Every 7 days
• Dosages (mcg/hr): 5, 7.5, 10, 15, 20 (max)
• Taper prior opioid to ≤30 MME before starting buprenorphine
Methadone is Different

The problem…

- Long, variable, unpredictable half-life
  - Analgesia 6-8 hours
  - Serum t½ 20-120 hours
- QTc prolongation, risk of torsades de pointes

Some possible advantages…

- NMDA receptor antagonist
  - Potentially less tolerance, better efficacy in neuropathic pain
- No active metabolites
- Inexpensive, small dosage units (5mg tablets)

## Dual Mechanism Opioids

<table>
<thead>
<tr>
<th>Tramadol</th>
<th>Tapentadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Weak mu-opioid agonist and NE and serotonin reuptake inhibitor</td>
<td>- Stronger mu-opioid agonist and NE reuptake inhibitor</td>
</tr>
<tr>
<td>- Seizure risk</td>
<td>- Seizure risk</td>
</tr>
<tr>
<td>- Physical dependence</td>
<td>- Physical dependence</td>
</tr>
<tr>
<td>- Not scheduled as controlled substance BUT has addiction potential</td>
<td>- Schedule II controlled substance with addiction potential</td>
</tr>
<tr>
<td>- Has a maximum therapeutic dose of 400mg per day</td>
<td></td>
</tr>
</tbody>
</table>
Opioid Safety and Risks

Allergies: Rare

Immunosuppression
- Animal models, opioid induced immuno-suppression
- Humans increased risk invasive pneumococcal disease\(^1\), community acquired pneumonia\(^2\)

Organ Toxicities
- Suppression of hypothalamic-pituitary-gonadal axis
- >50 MME associated with 2 fold increase fracture risk\(^3\)

Adverse Effects
- Nausea, sedation, constipation, urinary retention, sweating
- Pruritus (histamine release)
- Respiratory depression

Report AE to FDA
1-800-FDA-1088
www.fda.gov

2008

Respiratory Depression

- Depression of the medullary respiratory center
- Decreased tidal volume and minute ventilation
- Right-shifted CO$_2$ response
- Hypercapnea, hypoxia and decreased oxygen saturation
- Immediately life threatening
- Sedation occurs before significant respiratory depression and therefore is a warning sign

Managing Opioid Adverse Effects

**Nausea and vomiting**
- Usually resolves in few days; antiemetics, switch opioids

**Sedation**
- Mostly during initiation or change in dose
- Decrease dose

**Constipation***
- Most common and should be anticipated
- Stool softeners, osmotic stimulants, peripherally-acting mu-opioid antagonists, switch opioids; avoid bulking agents

**Pruritus**
- Switch opioids, antihistamines

**Urinary Retention**
- Switch opioids


*Hanson B et al. *Gastroenterology.* 2019
Medication-related Risk Factors

<table>
<thead>
<tr>
<th>Medication Factors</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose &gt;100 MME</td>
<td>Overdose</td>
</tr>
<tr>
<td>Long-term opioid use (&gt;3 months)</td>
<td>Overdose</td>
</tr>
<tr>
<td>ER/LA opioid formulation</td>
<td>Overdose</td>
</tr>
<tr>
<td>Initial 2 weeks after starting ER/LA opioid</td>
<td>Overdose</td>
</tr>
<tr>
<td>Combination opioids and benzodiazepines</td>
<td>Overdose</td>
</tr>
</tbody>
</table>

**CDC Recommendation 11:**
Avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.


## Patient-related Risk Factors

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental health disorder (e.g. depression, anxiety)</td>
<td>Overdose</td>
</tr>
<tr>
<td>Substance use disorder (e.g., alcohol, tobacco, illicit and prescription drug)</td>
<td>Overdose</td>
</tr>
<tr>
<td>Family history of substance use disorder</td>
<td>Misuse</td>
</tr>
<tr>
<td>Adolescent</td>
<td>Addiction</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>Overdose</td>
</tr>
<tr>
<td>Sleep-disordered breathing</td>
<td>Overdose</td>
</tr>
<tr>
<td>Legal history (e.g., DUI, incarceration)</td>
<td>Misuse</td>
</tr>
<tr>
<td>History of sexual abuse</td>
<td>Misuse</td>
</tr>
<tr>
<td>History of overdose</td>
<td>Overdose</td>
</tr>
</tbody>
</table>

Ives J, et al. *BMC Health Serv Res*. 2006  
High Dose Opioids

>90* mg morphine equivalents

Considered higher dose opioid therapy by different authors1,2,3

*Sample morphine equivalents:
90mg morphine = 60mg oxycodone, 22mg hydromorphone, 90mg hydrocodone

Higher doses indicated in some patients

- Manage as higher risk
- Increase monitoring and support

Higher doses more likely associated with:

- Tolerance4
- Hyperalgesia5,6
- Reduced function7,8
- Overdose9-13

Source of Prescription Opioids Misused

- Given by, Bought from, or Took from a Friend or Relative: 51.3%
- From Friend or Relative for Free: 38.6%
- Bought from Friend or Relative: 9.5%
- Took from Friend or Relative without Asking: 3.2%
- Some Other Way: 4.6%
- Bought from Drug Dealer or Other Stranger: 6.5%
- Got through Prescription(s) or Stole from a Health Care Provider: 37.6%
- Prescription from One Doctor: 34.7%
- Stole from Doctor’s Office, Clinic, Hospital, or Pharmacy: 0.9%
- Prescriptions from More Than One Doctor: 2.0%

SAMHSA 2019. Results from the 2018 National Survey on Drug Use and Health
Collateral Opioid Risk

• **Risks**
  - Young children’s ingestion and overdose
  - Adolescent experimentation leading to overdose and addiction

• **Mitigating risk**
  - Safe storage and disposal (i.e., lock box)
  - Educate family members
  - Have poison control number handy
  - Naloxone distribution (if available)*

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* Beletsky L, Rich JD, Walley AY. *JAMA* 2012; 308(18):1863-4
* SAMHSA Overdose Toolkit (http://store.samhsa.gov/shin/content/SMA13-4742/Toolkit_Patients.pdf)
* www.prescribetoprevent.org
INITIATION OF OPIOIDS
General Principles

- Initial course of treatment should be viewed as a short-term (<60 days), therapeutic trial
- Start low and titrate cautiously
- Avoid doses >90 mg morphine equivalent dose (MED)
- Opioid selection and initial dosing should be individualized based on
  - Patient’s health status (age, comorbid conditions)
  - Previous exposure to opioids (i.e. opioid tolerance)
- Do not start ER/LA formulations in opioid naïve patients
General Principles, continued

- Immediate release opioids provide pain relief between 3-6 hours
- ER/LA opioids provide analgesia between 6-24 hours depending on the formulation
General Criteria for Opioid Tolerance

- Based on daily use for more than 7 days
  - 60mg oral morphine per day
  - 30mg oral oxycodone per day
  - 25mcg transdermal fentanyl per 72 hours
  - 8mg oral hydromorphone per day
  - 25mg oral oxymorphone per day
Opioid Characteristics
Schedules of Administration

Intermittent Bolus Administration
Long-acting, CR meds

CNS side effects
(Reward, sedation, etc)

- Pain
- Withdrawal if opioid dependent

Analgesia

Plasma Concentration

Time
## Initiation of Opioids: IR Formulation

### Key Principles

**Immediate Release Opioid** | **Typical Starting Dose** | **Considerations**
--- | --- | ---
Codeine (oral) | 30mg every 4-6 hours | -Typically a combination product  
- Low potency opioid  
- Avoid concurrent use of OTC products  

Hydrocodone/acetaminophen (oral) | 5mg of hydrocodone every 4-6 hours | -Efficacy >40mg in question  
- Moderate potency opioid  
- Avoid concurrent use of OTC products  

Hydromorphone (oral) | 2mg every 4-6 hours | -High potency opioid  
- Should not be your first choice in IR opioids  

Morphine IR (oral) | 10mg every 4-6 hours | -Moderate potency opioid  
- Do not use in patient with CKD stage 4-5  

Oxycodone (oral) | 5mg every 4-6 hours | -Moderate potency opioid  

Oxymorphone (oral) | 5mg every 4-6 hours | -High potency opioid  

Tapentadol | 50mg every 12 hours | -Low potency opioid  
- Avoid concomitant serotonin products  

Tramadol | 25mg oral once daily | -Poor efficacy at doses >400mg  
- Low potency opioid  
- Avoid concomitant serotonin products  

*May be lower in patients with renal failure, hepatic failure, or age >65*
Initiation of ER/LA Opioids: Key Principles

*not for initiation in opioid naïve patients*

<table>
<thead>
<tr>
<th>ER/LA Opioid</th>
<th>Typical Starting Dose*</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine (Transdermal)</td>
<td>5mcg/hr patch every 7 days</td>
<td>-Should be off of other opioids for at least 5-7 days and not taking &gt;30mg MED</td>
</tr>
</tbody>
</table>
| Fentanyl (Transdermal)       | 12mcg/hr patch every 72 hours | -High potency opioid  
                             | -Use only in opioid-tolerant patients taking >60mg MED for a week or longer |
| Hydrocodone ER               | 10mg every 12 hours     |                                                                       |
| Hydromorphone ER             |                        |                                                                       |
| Methadone                    | 2.5mg TID              | See next slide                                                        |
| Morphine ER/LA               | 15mg every 12 hours     | -Moderate potency opioid                                               |
| Oxycodone ER/LA (oral)       | 10mg every 12 hours     | -Moderate potency opioid                                               |
| Oxymorphone ER/LA (oral)     | 10mg every 12 hours     | -High potency opioid                                                   |
| Tapendatol ER                | 50mg every 12 hours     | -Avoid concomitant serotonin products                                  |
| Tramadol ER                  | 100mg once daily        | -Poor efficacy at doses >400mg                                          |
|                              |                        | -Low potency opioid                                                   |
|                              |                        | -Avoid concomitant serotonin products                                  |

*May be lower in patients with renal failure, hepatic failure, or age >65*
Initiation of Methadone

• Start at low doses, individualized based on prior opioid exposure. Obtain baseline ECG due to QTc prolongation risk.
  - Chronic pain in opioid-naïve adults (or <40-60mg MED)
    - starting dose 2.5mg TID
    - Dose increases no more than 5mg/day every 5-7 days
  - Should not be started for opioid use disorder outside of an opioid treatment program

Resources on Specific Opioids

**Providers**
- e.g., dosing, specific product risks, limitations for use in patients with gastrointestinal problems such as inability to swallow, feeding tubes or malabsorption issues
- [dailymed.nlm.nih.gov/dailymed](dailymed.nlm.nih.gov/dailymed)
- [https://www.accessdata.fda.gov/scripts/cder/daf/](https://www.accessdata.fda.gov/scripts/cder/daf/)
- Package inserts on ER/LA website
- Adverse events to be reported to FDA [https://www.fda.gov/Drugs/InformationOnDrugs/ucm135151.htm](https://www.fda.gov/Drugs/InformationOnDrugs/ucm135151.htm)

**Patients**
- e.g., side effects, drug-drug interactions including CNS depressants, safe disposal
- Materials: [er-la-opioidrems.com/1wgUI/rem/products.action](er-la-opioidrems.com/1wgUI/rem/products.action)
- Medication guide given at the pharmacy
Calculating Morphine Equivalent Dose

**DO NOT USE FOR OPIOID ROTATION**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Conversion factor*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Fentanyl transdermal (in mcg/hr)</td>
<td>2.4</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>4</td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td>1–20 mg/day</td>
<td>4</td>
</tr>
<tr>
<td>21–40 mg/day</td>
<td>8</td>
</tr>
<tr>
<td>41–60 mg/day</td>
<td>10</td>
</tr>
<tr>
<td>≥61–80 mg/day</td>
<td>12</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>3</td>
</tr>
<tr>
<td>Tapentadol†</td>
<td>0.4</td>
</tr>
</tbody>
</table>


CDC Mobile App: https://www.cdc.gov/drugoverdose/prescribing/app.html
Calculating Morphine Equivalent Dose

- Fentanyl 25mcg/hr patch
  - 25 x 2.4 conversion factor (CF) = 60mg MED

- Hydromorphone 2mg every 4 hours + Oxycodone 60mg BID
  - 2mg x 6 = 12mg x 4 CF = 48mg MED
  - 60mg x 2 = 120mg x 1.5 CF = 180mg MED
  - TOTAL 228mg MED

- Methadone 20mg TID
  - 20mg x 3 = 60mg x 10.0* CF = 600mg MED

CDC Mobile App:
https://www.cdc.gov/drugoverdose/prescribing/app.html
# Overdose Risk Increases with Dose


<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>VA patients (fatal overdose)</th>
<th>Hazard ratio (95% CI)</th>
<th>HMO patients (any overdose)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>20-49</td>
<td>1.9 (1.3, 2.7)</td>
<td>1.4 (0.6, 3.6)</td>
<td>3.7 (1.5, 9.5)</td>
<td></td>
</tr>
<tr>
<td>50-99</td>
<td>4.6 (3.2, 6.7)</td>
<td></td>
<td>3.7 (1.5, 9.5)</td>
<td></td>
</tr>
<tr>
<td>≥ 100</td>
<td>7.2 (4.9, 10.7)</td>
<td>8.9 (4.0, 19.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case 1

- Patient has constant pain, but he self-manages
- He is not opioid tolerant
- He is asking for an opioid for activity PRN
- Best initial choice = IR formulation of tramadol, oxycodone, or hydrocodone dosed once-twice daily PRN activity
- Prescribe #28 per month to determine his response to treatment and opioid usage
Case 1

• If his pain were to progress and he started to need IR formulations of opioids around the clock, when would you transition to ER/LA formulation?
  ▪ When he is having worsening pain on a consistent basis when the opioid dose wears off
  ▪ When he develops opioid tolerance
  ▪ If his pain progresses
Case 1

- You decide to switch him from IR oxycodone 10mg every 6 hours PRN to ER/LA oxycodone 20mg BID

- He will utilize self-management techniques for breakthrough pain
OPIOID ROTATION

*If you are not experienced in switching opioids in patients on long-term opioid therapy, seek expert consultation.
Opioid Rotation

Definition and Purpose

- Defined *switching from one opioid to another to improve therapeutic outcome and/or to avoid adverse events due to the current drug*
- Theory
  - Variations in activity at mu opioid receptors may lead to improved benefit vs development of AE

Considerations

- Patient wishes/therapy adherence
- Cost/insurance concerns
- Titration leading to AE/poor analgesia
- Drug-drug interactions

Consider Opioid Rotation

• Switch to another opioid to:
  – Restore analgesic efficacy
  – Limit adverse effects
  – Decreasing overall MME

• Based on large intra-individual variation in response to different opioids
• Different variants of mu-opioid receptors
• Based on surveys and anecdotal evidence
• Promising but needs validation

Inturrisi CE. Clin J Pain. 2002
Smith HS, Peppin JF. J Pain Res. 2014
Opioid Conversion Tables

- Derived from relative potency ratios using single-dose analgesic studies in opioid-naïve patients
- Based on limited doses or range of doses
- Does not reflect clinical realities of chronic opioid administration
- Are not reliable due to individual pharmacogenetic differences
- Most tables do NOT adjust for incomplete cross-tolerance

Webster LR, Fine PG. *Pain Med.* 2012
Variable Response to Opioids

Mu-opioid Receptor
- >100 polymorphisms in the human MOR gene
- Mu-opioid receptor subtypes

Opioid Pharmacokinetiics
- Opioid metabolism differs by individual opioid and by individual patient

Not all patients respond to the same opioid in the same way

Trial of several opioids may be needed to find acceptable balance between analgesia and tolerability
WARNING!

Equianalgesic ≠ Conversion Tables

- Equianalgesic tables provide insufficient guidance to determine the equivalent doses of different opioids
  - Individual consideration is necessary for every patient

Opioid Rotation

- Seek expert advice if you are not experienced switching opioids in patients prescribed long-term opioid therapy.
- Calculate current Morphine Equivalents per day using an opioid conversion calculator
  - One example here
- For all opioids other than fentanyl or methadone, apply an “automatic dose reduction window” of 25-50% lower than the calculated equianalgesic dose
- Stop previous opioid and start new opioid (do not overlap doses)
- Reassess the patient frequently

Methadone Rotation

• Opioid rotation from <40-60mg MED
  ▪ Start methadone at 2.5mg TID
  ▪ Initial dose increases no more than 5 mg/day every 5-7 days

Methadone Rotation

• Opioid rotation from >60mg MED

  ▪ Start methadone at a dose 75-90% less than the calculated equianalgesic dose, but no higher than 30-40mg/day

  ▪ Initial dose increases no more than 5-10mg/day every 5-7 days

  ▪ Much lower doses are prescribed when switching to methadone due to incomplete cross tolerance and the long half-life of methadone

Case 1: Rotation Option 1

- After 1 year, the patient’s analgesic response to oxycodone ER 20mg BID wanes
- You decide to switch him to Morphine ER 15mg BID – a dose that is corrected by 50% for incomplete tolerance
  - [https://www.cdc.gov/drugoverdose/prescribing/app.htm](https://www.cdc.gov/drugoverdose/prescribing/app.htm)
- Patient Instructions:
  - Stop Oxycodone ER 20mg BID and wait 12 hours
  - Start Morphine ER 15mg BID
DISCONTINUING OR TAPERING OPIOIDS
Step 1: Evaluate Risks and Benefits, Establish an Indication for Opioid Tapering

- Substance Use Disorder
  - including opioids, alcohol, etc.
- Diversion
- At risk for immediate harms
  - Aspiration, hypoxia, bowel obstruction, overdose, etc.
  - Refusing monitoring (urine drug testing, abstain from marijuana or alcohol, etc.)
- Therapeutic Failure of opioids
- At risk for future harms (>90 MED, benzos)
  - High dose chronic use without misuse
  - Concomitant benzos
Use a Risk-Benefit Framework

NOT...

• Is the patient good or bad?
• Does the patient deserve opioids?
• Should this patient be punished or rewarded?
• Should I trust the patient?

RATHER...
Do the benefits of opioid treatment outweigh the untoward effects and risks for this patient (or society)?
Discontinuing Opioids

- Do not have to prove addiction or diversion - only assess and reassess the risk-benefit ratio
- If patient is unable to take opioids safely or is nonadherent with monitoring then discontinuing opioids is appropriate even in setting of benefits
- Need to determine how urgent the discontinuation should be based on the severity of the risks and harms
- Document rationale for discontinuing opioids
- Determine if the opioid needs to be tapered due to physical dependence

You are abandoning the opioid therapy **NOT** the patient
Step 2: Taper Plan and Start Taper

- Discuss goals of taper — how and when will we know if it is successful?
  - Establish dose target and timeframe
  - Maintain current level of analgesia (*may not be possible in short term*)

- Discuss potential withdrawal symptoms
  - Temporary increase in pain
  - Discuss how to contact
  - Schedule follow-up or nurse check-ins

- Identify at least one self-management goal
# How to Approach an Opioid Taper/Cessation

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Length of Taper</th>
<th>Intervention/Setting</th>
</tr>
</thead>
</table>
| **Substance Use Disorder**     | Recommend immediate referral and initiation of treatment | **Intervention:** Transition to medication assisted treatment (buprenorphine or methadone) maintenance therapy, Naloxone rescue kit  
**Setting:** Inpatient or Outpatient Buprenorphine (OBOT) or methadone |
| **Diversion**                  | No taper*                  | Determine need based on actual use of opioids, if any                                           |
| **At risk for immediate severe harms** | Weeks to months          | **Intervention:** Supportive care  
Naloxone rescue kit  
**Setting:** Outpatient opioid taper |
| **Therapeutic failure**        | Months                     | **Intervention:** Supportive care  
Naloxone rescue kit  
**Setting:** Outpatient opioid taper  
**Option:** Buprenorphine (OBOT) |
| **At risk for smaller harms**  | Months to Years            | **Intervention:** Supportive care  
Naloxone rescue kit  
**Setting:** Outpatient opioid taper  
**Option:** Buprenorphine (OBOT) |
Outpatient Tapering Options

• Gradual taper:
  ▪ 5-10% decreases of the original dose every 5-28 days until 30% of the original dose is reached, then weekly decreases by 10% of the remaining dose
  ▪ You may elect to taper Extended release (ER) or Immediate release (IR) first, though I generally taper ER first and use IR for breakthrough pain
  ▪ Provide the patient a copy of the taper plan for reference and to help keep patient moving forward
Outpatient Tapering Options

- Rapid taper:
  - Daily to every other day reductions over 1-2 weeks as appropriate

- Initiation of Medication for Opioid Use Disorder
  - Adjuvant opioid withdrawal medications only
  - Office based buprenorphine treatment transition
  - Methadone treatment, refer to opioid treatment program
### Adjuvant Opioid Withdrawal Medications

<table>
<thead>
<tr>
<th></th>
<th>Geriatric (&gt;65 years) Considerations</th>
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<tbody>
<tr>
<td><strong>For sweating, anxiety, agitation</strong></td>
<td>Do not use if baseline SBP &lt; 110</td>
</tr>
<tr>
<td>Clonidine 0.1mg by mouth three times daily PRN anxiety</td>
<td>Caution with patients who are at risk for falls (On Beers list)*</td>
</tr>
<tr>
<td>Hold for sedation or dizziness</td>
<td></td>
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<tr>
<td><strong>For anxiety</strong></td>
<td>Hydroxyzine 12.5-25 mg by mouth every 8 hours PRN anxiety</td>
</tr>
<tr>
<td>Hydroxyzine 25-50 mg by mouth every 4-6 hours PRN anxiety</td>
<td>Increased potential for anti-cholinergic side effects (on Beers list)</td>
</tr>
<tr>
<td><strong>For nausea or vomiting</strong></td>
<td>Alternative: Zofran 4 mg by mouth every 12 hours PRN for nausea or vomiting</td>
</tr>
<tr>
<td>Phenergan 12.5-25 mg by mouth every 4-6 hours PRN nausea/vomiting</td>
<td>Phenergan associated with anticholinergic side effects and somnolence in older adults (on Beers list)</td>
</tr>
<tr>
<td>OR Zofran 4mg every 12 hours PRN nausea/vomiting</td>
<td>Caution with patients who are at risk for falls</td>
</tr>
<tr>
<td><strong>For abdominal cramping/diarrhea</strong></td>
<td>Avoid use in this age group due to potent anticholinergic side effects and uncertain effectiveness (on Beers list).</td>
</tr>
<tr>
<td>Hyocosamine 0.125mg by mouth every 4-6 hours PRN abdominal cramping</td>
<td></td>
</tr>
<tr>
<td><strong>For increased pain with taper and from opioid withdrawal</strong></td>
<td>Alternative: Acetaminophen 1000 mg by mouth three times daily if not contraindicated</td>
</tr>
<tr>
<td>Ibuprofen 400-600 mg by mouth three times daily PRN with food and water for pain</td>
<td>Ibuprofen contraindicated in chronic kidney disease, history of GI bleed, chronic warfarin use, etc. (on Beers list)</td>
</tr>
<tr>
<td>OR TYLENOL 500mg by mouth every 4-6 hours PRN pain</td>
<td>(Maximum dose 3,250mg in 24 hours)</td>
</tr>
</tbody>
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*The AGS 2012 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (AGS 2012 Beers Criteria) J Am Geriatr Soc. 2012 Apr;60(4):616-31

**It is not legal or safe to prescribe Methadone for opioid withdrawal in the outpatient setting.**

**It is not advised to prescribe benzodiazepines for opioid withdrawal.**
Step 3: Provider Self-Care

- Check in with a colleague
- Process what went well and what was hard
- Develop an “opioid committee” to support you and the clinic

You are abandoning the opioid therapy **NOT** the patient
Some patients will struggle with an opioid taper. Continually evaluate the risks and benefits.

- Methadone >30mg
- MED >200mg
- Long term use > 5 years
- Mental illness, distress intolerant, history of adverse childhood experiences, history of substance use disorder, weak social supports

Buprenorphine/naloxone is an important resource for these patients

Also consider interdisciplinary pain programs
Case 2: Immediate Risks

50 yo man on opioids for LBP x 5 years develops severe constipation that is not amendable to treatments. You decide the risks outweigh the benefit of him remaining on morphine ER 15mg BID.

- **Taper Plan:**
  - Step 1: convert his morphine to IR and reduce it to morphine IR 7.5mg Q8H for 2 weeks
  - Step 2: Reduce morphine IR 7.5mg BID for 2 weeks
  - Step 3: Morphine IR 7.5mg daily for 2 weeks
  - Step 4: stop morphine
Case 3: Immediate Risks

• What if that same 50 yo man on opioids for LBP x 5 years is prescribed fentanyl 75mcg/72 hours.

• **Taper Plan:**
  - Step 1: convert his fentanyl to a different opioid that is easier to taper like morphine ER or oxycodone ER. Ex. Morphine ER 45mg/30mg/30mg.
  - Step 2: Morphine ER 30/30/30mg TID x 2 weeks – 1 mo
  - Step 3: Continue in 10-20% reductions until done
Case 4: Substance Use Disorder

50 yo male prescribed hydromorphone 4mg every 3 hours and fentanyl 50mcg patch for chronic pancreatitis. You detect alcohol on a routine urine drug screening, and he admits that he has had a recurrence of his alcohol use disorder.

• What do you do?
  ▪ Decide that the risks greatly outweigh the benefit
  ▪ Refer to detoxification from alcohol and opioids
  ▪ Evaluate opioid dose for safety and taper accordingly
Case 5

28 yo female prescribed opioids for chronic abdominal pain. She states she has lost her opioid prescription for the third time. She has had two negative urine drug tests for the opioid that is prescribed and refuses to come in for a pill count.

- You suspect diversion.
- Taper Plan: None. You stop prescribing opioids immediately.
Case 6: Long term opioid therapy with therapeutic alliance

68 yo female with rheumatoid arthritis pain. She is prescribed a total of 350mg MED for the last 5 years with no adverse events. She is moderately functional. Your clinic has developed a new opioid policy stating that patients prescribed doses >120mg MED need to attempt an opioid taper. She is concerned that she might develop serious harms from her opioids.

- **Taper plan:** Slow taper by 10% per month over a year. May elect to slow down the taper if she experiences periods of worsening pain and/or opioid withdrawal.
- Provide education about opioid overdose and naloxone rescue kit.
Case 7: Long term opioid therapy with difficult therapeutic engagement

63 yo man with history of low back pain and severe depression after a work injury in 1982. He has not worked since and spends most of his day being sedentary. He has been unwilling to engage in additional pain modalities despite multiple offers. He is prescribed oxycodone IR 30mg every 4 hours. You have tried other opioids but he has not had improvements. He refuses an opioid taper and states he will seek another provider if you start to taper his opioids.

- **Taper Plan:** Offer buprenorphine OR a 1 month rapid taper
- Provide education about opioid overdose and naloxone rescue kit.
Risk Benefit Framework

Useful in Decision to Continue or Discontinue Opioids

Benefits
- Pain
- Function
- Quality of Life

Risks/Harm
- Misuse
- Addiction, Overdose
- Adverse Effects

Useful to Avoid Pitfalls
- “But I really, really need opioids.”
- “Don’t you trust me?”
- “I thought we had a good relationship/I thought you cared about me.”
- “If you don’t give them to me, I will drink/use drugs/hurt myself.”
- “Can you just give me enough to find a new doc?”

RESPONSE: “I cannot continue to prescribe a medication that is not helping you (or is hurting you or both).”
Summary

- Several different formulations and routes of opioids are available. It is important to understand these differences in order to safely prescribe the medications.

- Patients can benefit from opioid rotation to achieve better pain control and less side effects, but clinical experience is needed to ensure a safe opioid transition.

- Tapering opioids can be a challenging process, but general principles can help promote success.

- In the right situation, allowing a patient to share some decision making about the opioid taper can help a taper’s success.

- There will be several occasions where shared decision making about the opioid taper is not possible.

- See also Scope of Pain
References

- National Survey on Drug Use and Health: SAMHSA, Office of Applied Studies; 2011
PCSS Mentoring Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid use disorder.

- PCSS Mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medications for opioid use disorder (MOUD).

- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.

- No cost.

For more information visit: [https://pcssNOW.org/mentoring/]
PCSS Discussion Forum

Have a clinical question?

Ask a Colleague

A simple and direct way to receive an answer related to medications for opioid use disorder. Designed to provide a prompt response to simple practice-related questions.

http://pcss.invisionzone.com/register
PCSS is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

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