1. Evidence for opioid use in chronic pain

**Precourse Objective:** Understand the breadth and quality of evidence behind use of opioids for chronic pain, as well as current gaps in knowledge

**Principles:**
- Pain reduction achieved during short duration of trials was, on average, about 30%
- Limited data on on functional improvement with opioids
- Lack evidence of superiority of one long-acting opioid over another
- Lack evidence of superiority of long-acting opioids to short-acting opioids
- Lack evidence of superiority of long-acting opioids over other pain agents
- Lack evidence as to superiority in efficacy and safety
- High discontinuation rates in the studies: adverse effects + lack of efficacy
- Limited data on long-term efficacy of opioids
- Most studies exclude patients with history of substance abuse or addiction

**Bottom line:**
- Treatment decisions should be based on risk-benefit ratio individualized for each patient based on clinical indication and assessment of risk for prescription drug misuse with opioid therapy for chronic noncancer pain.

**References**

2-10

**Precourse Objective:** List 4 patient-level goals in treating chronic pain with opioids

- Dispel unrealistic goals (complete pain relief)
- Reduced pain
- Improved function (specific)
- Improved mood
- Improved sleep
- Improved function at work (or moving toward reentering work force)

**Precourse Objective:** Identify appropriate opioid analgesic based on patient presentation as well as safety and efficacy data

Long-acting opioids can be effective in reducing pain and improving function in a variety of CNMP syndromes. Patients should be well-selected for opioid therapy; should be informed of the effects, side effects, and risks of treatment; should be monitored for improvement in pain and function; and should be monitored frequently for effects, side effects, and potential misuse. The medical record should provide clear documentation of this as well.
Principles of initiating long-acting medications used in CNMP

The 4 long-acting opioids used commonly in CNMP are FULL AGONISTS to the opioid receptor (mainly Mu). This means that there is no CEILING DOSE and that the dose can be escalated to pain relief limited only by side effects (and potential misuse). However, note that there is minimal evidence to support the use of unusually high doses of long-acting opioids when used for CNMP. All long-acting opioids are SCHEDULE II.

The CLASS of opioid is an important consideration if there is a true allergic reaction to 1 class of opioid as another class of opioid can be tried. Morphine ER and Oxycodone ER are both phenanthrenes while methadone and transdermal fentanyl are in separate classes.

There is wide INDIVIDUAL VARIABILITY in pain response to long-acting opioids as well as in side effect response.

- Part of this has to do with BIOAVAILABILITY:
  - A HIGHER BIOAVAILABILITY (higher %) means a more predictable response to the drug from patient to patient while a LOWER BIOAVAILABILITY (lower %) means a less predictable response.

- Part of this also has to do with METABOLISM:
  - Some have ACTIVE METABOLITES which are responsible for binding to the opioid receptors and producing pain relief while others have INACTIVE METABOLITES which have no effect on pain relief.
  - In general long-acting opioids are METABOLIZED in the liver and EXCRETED in the kidneys.
  - Liver METABOLISM of long-acting opioids is generally responsible for drug interactions if the opioid requires one of the P450 enzyme systems that other drugs may induce or inhibit.

- Because of this variability, TITRATING long-acting opioids is expected and should occur according to report of pain relief and increased function but not at an interval more frequent than it takes to reach a STEADY STATE (to avoid serious side effects such as respiratory depression).
- The concept of OPIOID ROTATION is based on the development of TOLERANCE to a particular opioid medication. When converting between opioid medications, there is variability in CROSS-TOLERANCE to the receptors and therefore, a conservative starting dose of long-acting opioid should be initiated with close monitoring for side effects and TITRATION as appropriate to steady state and pain control.
- Adverse reactions of opioid medications are generally NOT allergic reactions. They are common between opioids, however, there is drug variability as well as individual variability.

Morphine Extended Release: Morphine ER (generic), MS Contin, Avinza, Kadian, Oramorph SR

- 1st line in opioid-naïve patients
- Natural opioid: increased CNS and GI side effects (6-hydroxyl group)
- Full agonist at Mu, low bioavailability
- Glucuronidation to active metabolites (morphine-6-glucuronide, morphine-3-glucuronide)
- Few drug interactions

Oxycodone Extended Release: Oxycodone ER (generic) and Oxycontin

- 1st or 2nd line in opioid naïve patients
- Synthetic opioid (few adverse effects)
- Full agonist at Mu and Kappa
- Avoid in patients at moderate to high risk of prescription drug misuse
- High bioavailability, decreased side effects, ability to alter ER mechanism
- Converted to active metabolites via P450 2D6 liver enzyme system (oxymorphone)
- 5-10% of Caucasians have diminished 2D6 activity and thus may have reduced analgesia
- Inhibitors of 2D6 may decrease conversion to active metabolites: celecoxib, some SSRIs, amiodarone
Methadone: Methadone (generic), Methadose, Dolophine\textsuperscript{13-16}

- 1st line opioid for Neuropathic pain due to NMDA antagonist effects and patients moderate to high risk of prescription drug misuse (Lack of euphoria due to long half life and lack of ability to disrupt long-acting mechanism)
- Full agonist at Mu receptor
- Wide range of bioavailability (40-100%) so unpredictable patient response
- Half-life is 9 to 50 hours, steady state in 7-10 days
- Must start very low doses and titrate very slowly: dose-accumulating side effects due to long half-life
- Does not depend on active metabolites, is converted to inactive metabolites by multiple liver enzyme systems
- Drug interactions are significant

Black Box Warning for Methadone:
- Respiratory Depression
- “Methadone’s peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects.”
- Incomplete cross-tolerance
- Iatrogenic overdose
- Prolonged QT interval

Use Methadone with caution in patients with:
- Reduced clearance (liver insufficiency)
- Significant drug-drug interactions
- Other sedative medications including benzodiazepines, including alcohol
- Unreliable adherence to prescribed dosing (self-titration can cause serious/life-threatening adverse effects)
- History of arrhythmia (prolonged QT – Torsades de Pointes)

Fentanyl TTS (transdermal therapeutic system): Fentanyl TTS (generic available for most strengths except 12.5mcg/hr), Duragesic\textsuperscript{17,21}

- Potent opioid with high bioavailability
- Full agonist at Mu receptor
- Highly lipophilic (enhanced CNS side effects)
- Liver metabolism to inactive metabolites
- Some drug interactions:
  - Increase: some HIV medications, “azole,” “mycins,” and grapefruit juice
  - Decrease: carbamezepine, St. John’s wort
  - Develops subcutaneous reservoir after application, consistent release
Precourse Objective: Give an example of when short-acting and when long-acting opioids would be most appropriate

**Long- versus Short-acting Opioids based on Pattern of Pain**

<table>
<thead>
<tr>
<th>Opioid selection</th>
<th>Pattern of Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td>Trial of opioid medication to assess dosage needs (can then be converted to long-acting)</td>
</tr>
<tr>
<td></td>
<td>Temporary flares of intense pain with either no pain or tolerable pain in-between (chronic intermittent pain NOT breakthrough pain)</td>
</tr>
<tr>
<td></td>
<td>o A rapid-onset formulation may be considered for sudden onset pain to control it before reaching maximal intensity.</td>
</tr>
<tr>
<td></td>
<td>Short-acting opioids can be dosed around the control for persistent pain (in the place of long-acting opioids)</td>
</tr>
<tr>
<td>Long-acting plus short-acting</td>
<td><strong>Chronic persistent pain</strong> controlled on long-acting opioids, but with episodes of <strong>break through pain</strong></td>
</tr>
<tr>
<td></td>
<td>A rapid-onset formulation may be considered for sudden onset pain or intense flares of <strong>breakthrough pain</strong> to control it before reaching maximal intensity</td>
</tr>
<tr>
<td></td>
<td>Lower required long-acting opioid dosing may be achievable for background <strong>chronic persistent pain</strong> if <strong>breakthrough pain</strong> is effectively controlled</td>
</tr>
<tr>
<td>Long-acting</td>
<td>Failure of nonopioid treatment for <strong>chronic persistent pain</strong> without episodes of <strong>breakthrough pain</strong></td>
</tr>
<tr>
<td></td>
<td>Primary benefit of long-acting opioids in such settings is convenience of dosing</td>
</tr>
</tbody>
</table>

2. Side effects and “risks” of opioid use in chronic pain

Adverse Opioid Reactions

<table>
<thead>
<tr>
<th>System</th>
<th>Reaction</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Drowsiness, sedation, hallucinations</td>
<td>CNS side effects more common with morphine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolerance develops to sedation</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Respiratory depression</td>
<td>Tolerance develops to respiratory depression</td>
</tr>
<tr>
<td>Ocular</td>
<td>Miosis</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>Nausea, constipation, delayed emptying</td>
<td>Morphine/Codeine due to 6-hydroxyl group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydromorphone and oxycodone lack 6-hydroxyl group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolerance DOES NOT develop to constipation</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension, bradycardia</td>
<td>High opioid doses</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Muscle rigidity, myoclonus</td>
<td>High opioid doses</td>
</tr>
<tr>
<td>Immune</td>
<td>Pruritis from mast cell histamine release</td>
<td>Morphine/Codeine (natural opioids)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More common with IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolerance develops to pruritis</td>
</tr>
<tr>
<td>Physical dependence (results in withdrawal symptoms)</td>
<td>Results in withdrawal symptoms: restlessness, yawning, lacrimation, rhinorrhea, piloerection, perspiration, chills/myalgias</td>
<td></td>
</tr>
<tr>
<td>Tolerance (basis for opioid rotation)</td>
<td>Decreased duration of pain response over time</td>
<td>Decreased effectiveness of pain relief over time</td>
</tr>
</tbody>
</table>
3. **Regulatory Considerations**

**Legal Considerations in Controlled Substance Prescribing**
Adapted from *VCU Chronic Nonmalignant Pain Management*

A major barrier to the use of controlled substances in the treatment of chronic nonmalignant pain is the fear of law enforcement investigation. A survey of physicians reported that over half would reduce the dose or quantity, reduce the number of refills, or choose a medication in a lower schedule due to concerns about regulatory scrutiny. However, fewer than 1% of health care providers who prescribe controlled substances are ever investigated.

Both healthcare providers and law enforcement personnel share responsibility for assuring availability of prescription pain medications while preventing them from becoming a source of harm or abuse. In 1996, a consensus statement from the American Academy of Pain Medicine (AAPM) and the American Pain Society (APS) legitimized the use of opioids in chronic pain. Additionally, in 1998 the Federation of State Medical Boards released guidelines for the use of opioids in medical practice.

If providers consistently follow these guidelines, it is unlikely that an investigation will occur, and if it does occur, unlikely that it will result in significant consequences to the physician. In a recent review, Fishman states, "...physicians who maintain ongoing vigilance by exercising consistent and transparent risk management practices for all of their patients on opioid therapies are not at substantial risk of regulatory action".

4. **Benefit-risk framework and organizing principles**

**Precurso Objectives:**
- Understand a practical framework for making decisions regarding the initiation, maintenance, and discontinuation of opioid analgesics for the treatment of chronic pain
- Gain exposure to clinical tools and practice communication techniques that maximize benefit and minimize risk and achieve consistency in practice

**Essential Elements of Communication in Medical Encounters**

**Build the Relationship**
- Elicit the patient’s story of illness while guiding the interview through a process of diagnostic reasoning. It requires awareness that the ideas, feelings, and values of both the patient and the physician influence the relationship.

**Open the Discussion**
- Allow the patient to complete his or her opening statement
- Elicit the patient’s full set of concerns
- Establish/maintain a personal connection

**Gather Information**
- Use open-ended and closed-ended questions appropriately
- Structure, clarify, and summarize information
- Actively listen using nonverbal (e.g., eye contact) and verbal (e.g., words of encouragement) techniques

**Share Information**
- Use language the patient can understand
- Check for understanding
- Encourage questions

**Reach Agreement on Problems and Plans**
- Encourage the patient to participate in decisions to the extent he or she desires
- Check the patient’s willingness and ability to follow the plan
• Identify and enlist resources and supports

**Provide Closure**
• Ask whether the patient has other issues or concerns
• Summarize and affirm agreement with the plan of action
• Discuss follow-up (e.g., next visit, plan for unexpected outcomes)

5. **Safeguards in practice**

**Precourse Objective:** Recall appropriate assessment, monitoring and documentation strategies to meet best practice standards and medico-legal requirements to support opioid prescribing

**Assessment**
• Thorough history, particularly of pain and prior treatment
• Examination and appropriate diagnostic testing if indicated
• Multi-dimensional treatment approach
• Defined patient-centered outcome goals

**Opioid Assessment Screening Tools (OASTs)**
• Opioid Risk Tool
• The Screener and Opioid Assessment for Patients with Pain (SOAPP)\(^ {35-37}\)
• The Pain Medication Questionnaire (PMQ)\(^ {38-40}\)
• Opioid dependence or abuse based on DSM-IV criteria
• Screening Instrument for Substance Abuse Potential (SISAP)\(^ {41}\)
• CAGE questionnaire (Cut down, Annoyed, Guilt, and Eyeopener): adapted to include drugs (CAGE-AID)\(^ {5}\)
• Drug Abuse Screening Test (DAST)\(^ {42}\)
• Rapid Drug Problems Screen (RDPS)\(^ {43}\)

**Safe prescribing practices**
• Medicaid Tamper-Resistant Prescription Pads
• Keep prescription blanks in secure locations
• Do not leave in patient-accessible areas such as waiting rooms or examination rooms
• If appropriate, choose long-acting opioids and opioids of lesser street value
• Hand write prescriptions on watermark paper or prescription blanks
• Do not use adhesive labels; hand write patient name and date of birth
• Limit the quantity to no more than a 30-day supply or provide exactly enough medication until next follow-up appointment
• Use numbers and letters to document quantity and strength of medication
• Do not sign incomplete prescriptions
• Copy all controlled substance prescriptions for chart documentation
• If possible, allow only the patient to pick-up prescriptions
• Assist the pharmacist when they telephone to verify information

**Precourse Objective:** Name 2 practice-based tools that could be used to monitor patients for misuse of opioid analgesics

**Monitoring Strategies**\(^ {44}\)
• The Current Opioid Misuse Measure (COMM)\(^ {45}\)
• Pain Assessment and Documentation Tool (PADT)\(^ {46, 47}\)
  o Analgesia (pain relief)
  o Activities of daily living (psychosocial functioning)
  o Adverse effects
  o Aberrant medication taking
• Face to face office visits for monitoring and periodic reassessment
- Pharmacy records
- Prescription monitoring program data
- Urine drug screening
- Pill counts

**Office Practice Standards and Documentation**
- Office-wide controlled substance policy
- Office-wide controlled substance agreement with informed consent
- Office visit documentation templates
  - Pain Assessment and Documentation Tool (PADT)
  - Office visit new patient/follow-up templates
  - Controlled substance flow sheets (electronic or written)

**FSMB* Criteria when evaluating a physician’s treatment of pain**

<table>
<thead>
<tr>
<th>Evaluation of the Patient</th>
<th>H&amp;P including detailed history of pain Medical indication for use of controlled substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Plan</td>
<td>Objectives used to determine treatment success</td>
</tr>
<tr>
<td>Informed consent and agreement for treatment</td>
<td>Discussion of risks and benefits Consider use of a written agreement (Samples from AAPM)</td>
</tr>
<tr>
<td>Periodic Review</td>
<td>New health information Improvement, stability, or progression of pain Changes in treatment plan</td>
</tr>
<tr>
<td>Consultation if/when appropriate</td>
<td>Willingness to refer patients with complex issues or if not meeting treatment objectives</td>
</tr>
<tr>
<td>Accurate and complete medical records</td>
<td>Accessible documentation of criteria listed above</td>
</tr>
<tr>
<td>Compliance with laws and regulations</td>
<td>Licensed to dispense controlled substances</td>
</tr>
</tbody>
</table>

**Precourse Objective:** List 2 possible explanations for why a patient may exhibit aberrant opioid taking behaviors that are not due to drug addiction

**Differential Diagnosis of Aberrant Medication Taking Behavior**
- Inadequate pain management
  - Suboptimal analgesia
  - Progressive pathology
  - Opioid tolerance
  - Opioid induced hyperalgesia
- Inability to adhere to treatment
  - Self medication
  - Chemical coping
  - Psychiatric disease
  - Addiction
- Criminal Intent
  - Diversion by patient, theft by others
Precourse Objective: Give one reason for and one reason against using opioid agreements\textsuperscript{50, 54, 55}

- Widely used though efficacy not established
- Informed consent through written agreement
- Adherence to comprehensive treatment plan
- Clarify and describe “consequences” of AMTBs
- Exit strategy if patient not meeting treatment goals
- Specifics
  - Single provider & single pharmacy
  - No early refills or telephone refills
  - Pill-counts at visit (must bring bottles)
  - Periodic urine drug screening
  - Access prescription monitoring program (if available)

Precourse Objective: Give one reason for and one reason against using urine toxicology testing to monitor for prescription drug abuse\textsuperscript{56-59}

- 27\% of patients with no behavior signs suggestive of misuse had “inconsistent” UDS\textsuperscript{49}
- A powerful non “self-report” tool to assist in monitoring
- When ordering test, document last dose and last 24-48 hour quantity of substance
- Correct test must be ordered: Distinguish between “screening” and “confirmation” tests
  - Screening
    - Class of medications, generally immunoassays
    - Reported as “positive” or “negative,” varied minimum cutoff concentration
    - Frequently misinterpreted
  - Confirmation: confirms presence of actual substance or metabolite
    - Generally Gas Chromatography or Mass Spectroscopy, high-performance liquid chromatography
- What are you looking for?
  - Illicit substance, prescription drug misuse, presence of prescribed medication
  - Recommended: cocaine, amphetamines, opiates, methadone, marijuana, benzodiazepines
- Test must be accurately interpreted

<table>
<thead>
<tr>
<th>Prescribed Medication</th>
<th>Interpretation</th>
</tr>
</thead>
</table>
| Morphine              | General screen: opiates positive  
                        Specific screen: morphine, morphine-6-glucuronide, morphine-3-glucuronide, hydromorphone (if chronic, on high doses due to slow GI conversion)  
                        “False” positive: Heroin and codeine |
| Oxycodone             | General screen: Opioid negative at doses < 100-150mg/24 hours  
                        due to <10\% is excreted unchanged in the urine  
                        Sensitive/Specific screen: oxycodone and oxymorphone  
                        Can test for the combination drug (i.e. acetaminophen in Percocet) |
| Fentanyl              | Requires specialized testing using GC/MS  
                        General screen: opioid negative  
                        Specific screen: fentanyl, norfentanyl  
                        “False” positive: trazodone |
| Methadone             | Requires specific immunoassay  
                        General screen: opioid negative  
                        Specific/sensitive screen: methadone and methadone metabolite  
                        “EDDP” will be positive with average of 40mg/24 hours |
REFERENCES


