Prescriber Considerations When Treating Chronic Pain

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Roger Chou MD
Professor of Medicine
Oregon Health & Science University
Departments of Internal Medicine, and Medical Informatics & Clinical Epidemiology
Director, Pacific Northwest Evidence-based Practice Center
Conflict of interest disclosure

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Purpose

• Understand opioid prescribing patterns for pain
• Understand risks and benefits of long-term opioid therapy and non-opioid therapies for chronic pain
• Understand and apply strategies to more safely and effectively prescribe pharmacological therapies for the management of chronic pain
Case

53-year old female transferring care because her PCP is leaving practice

- Shoulder and hip pain 2° avascular necrosis, s/p shoulder replacements, hip decompression, hip replacement
- Fibromyalgia, non-radicular LBP, chronic headache
- Depression, fatigue
- Gastroparesis, irritable bowel syndrome
- Morphine IR 30 mg 5 T (150 mg) q 8 hrs + oxycodone 5 mg 8 T (40 mg) q 6 hrs
  - MED/day: 690 mg
- Provigil 20 mg po qD
- Pain 6/10 on average, with day to day fluctuation
- Can carry out ADLs with pain, limited exercise, no aberrant behaviors
Background

• Chronic noncancer pain highly prevalent, with substantial burdens
  • Estimates vary, up to 1/3 of adults report some CNCP
• Opioids have become commonly prescribed for chronic noncancer pain
  • About 5% of adults report use of LOT\(^a\)
  • The U.S. is \(~5%\) of the world’s population, but accounts for 80% of the world’s supply of opioids (99% of hydrocodone)
• Opioids are associated with potential harms, both to patients and to society
Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010)

Prescription opioid prescribing patterns

Some states have more painkiller prescriptions per person than others.

Number of painkiller prescriptions per 100 people
- 52-71
- 72-82.1
- 82.2-95
- 96-143

SOURCE: IMS, National Prescription Audit (NPA™), 2012.
Opioid pharmacology

- Opioid mu-receptors mediate analgesic effects and AE’s
  - Agonists, partial agonists, antagonists
  - Natural, semisynthetic, synthetic
  - Half-life 2-4 hours for most opioids; 15-30 hours for methadone
- Ongoing exposure causes tolerance
  - Larger dose required to maintain original effects (analgesic and AE’s)
  - Interindividual 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.”
- **No theoretical dose ceiling**

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\(^a\)Inturrisi C. Clin J Pain 2002;18:S3-13
Dose-response relationship for respiratory depression

A

Ventilation (L/min)

Fentanyl dose (μg/kg)

B

Ventilation (L/min)

Buprenorphine dose (μg/kg)
Prescribing trends

• 1980 vs. 2000: Opioid use for chronic pain increased from 8% to 16%
• Use of more potent opioids increased from 2 to 9%
• Greatest increase in daily doses occurred in schedule II opioids
• Trends observed across age groups and in men and women
• Trends observed among commercial insurance and Medicaid populations

How did we get here?

- Perceived undertreatment of chronic pain
  - Laws or regulations passed in >20 states to allow use of opioids for chronic pain
- Low risk of abuse observed with use of opioids in palliative care settings
  “…patients rarely demonstrate euphoric responses to opioid drugs, and neither analgesic tolerance nor physical dependence is a significant clinical problem.”
- Case series describing benefits of long-term opioid therapy for chronic pain, with low rates of abuse, addiction, or other serious AE’s
  - Most prescribed low doses (<20 mg MED/day)
- No ceiling dose used in palliative care settings
  - “Escalation of the opioid dose until either adequate analgesia occurs or intolerable and unmanageable side effects supervene is standard practice in cancer pain management.”
  - Emphasis on round-the-clock dosing using sustained-release formulations

\[a^{Portenoy RK. J Law Medicine Ethics 1996;24:296}\]
\[c^{Portenoy RK. J Pain Symptom Management 1996;11:203}\]
Evidence on effectiveness of LOT for chronic non-cancer pain

- **Short-term efficacy**
  - 62 RCT’s in one recent meta-analysis, duration <16 weeks in 61
  - Opioids more effective than placebo for nociceptive and neuropathic pain (effect sizes 0.55-0.60)
  - Maximum dose ≤180 mg MED/day in all trials except for 3

- **Long-term effectiveness**
  - No placebo-controlled trial >6 months
  - Cochrane review included 26 studies >6 months
    - 25 studies were case series or uncontrolled long-term trial continuations
    - Many discontinuations due to adverse effects (23%) or insufficient pain relief (10%)
    - Some patients who continued on opioids reported long-term pain relief (but no control group); no evidence on function

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\(^{a}\)Furlan et al. Pain Res Manag 2011

\(^{b}\)Noble et al. Cochrane Database Syst Rev 2010
Other limitations of the evidence on effectiveness of LOT

- Effects on function generally smaller than effects on pain; some trials showed no or minimal benefit
- High loss to follow-up
- Trials typically excluded patients at higher risk for abuse or misuse, psychological comorbidities, and serious medical comorbidities
- Limited evidence on commonly treated conditions
  - Low back pain, fibromyalgia, headache, others
- No trials of LOT vs. CBT-based exercise therapy or interdisciplinary rehabilitation
Factors associated with increased risk of overdose, or observed in high proportions of overdoses

- Aberrant behaviors
- Recent initiation of opioids
- Methadone
- Concomitant use of benzodiazepines
- Obtaining opioid prescriptions from multiple providers
- Substance abuse and other psychological comorbidities
- Higher dose
• Observational studies consistently show an association between opioid dose and risk of overdose or death in patients with chronic pain.
• Risk starts to increase at relatively low doses and continues to increase.
• Studies matched or adjusted for potential confounders available in administrative databases.
• Difficult to determine whether patients had chronic pain and duration of therapy.
• One RCT found no difference between more liberal dose escalation vs. dose maintenance strategies, but limited separation of doses (mean 52 vs. 40 mg MED/day)\(^a\).
• Patients who do not respond to lower doses may not respond to higher doses.

\(^a\)Nabiloff BD. J Pain 2011;12:288
Dose-related risk of opioid overdose

Risk of adverse event

Risk Ratio

Dose in mg MED

<20 mg/day 20-49 mg/day 50-99 mg/day >=100 mg/day

Risk Ratio

0 1 2 3 4 5 6 7 8 9 10

Dunn 2010
Bohnert 2011
Gomes 2011
Zedler 2014
• Opioid abuse or dependence diagnosis (vs non-use) (Edlund MJ. Clin J Pain 2014;30:557)
  • Low dose (1-36 mg MED/day): OR 15 (95% CI 10 to 21)
  • High dose (≥120 mg MED/day): 122 (95% CI 73 to 206)
• GI, cognitive, rash
• Endocrinological
  • Lab evidence of hypogonadism, association with use of testosterone or meds for erectile dysfunction
• Fracture
• CV events
• Dose-response relationship for some harms

Other harms of opioid therapies
### Dose threshold policies

- **2007**: Washington Agency Medical Directors’ Opioid Dosing Guidelines
  - 120 mg MED/day threshold dose
- **2009**: APS/AAPM guideline
  - 200 mg MED/day “watchful” dose
- Subsequent policies have generally recommended dosing thresholds of 80-120 mg/day MED; as low as 50 mg/day MED
- **2016 draft CDC guideline**
  - “Caution” with doses >50 mg/day MED
  - “Avoid” doses >90 mg/day MED

*Franklin et al, Am J Industrial Med 2011*
Mitigating risks associated with use of opioids

- Monitoring, including urine drug testing
- Access prescription drug monitoring data
- Avoid sedative-hypnotics (particularly benzodiazepines)
- More frequent follow-up
- Addiction, pain, or psychiatric consultation
- More frequent refills with smaller quantities
- Abuse-deterrent formulations
- Naloxone co-prescription
Non-opioid medics
- Analgesics: Acetaminophen, NSAIDs
- Antidepressants: SNRI’s, TCA’s
- Gabapentin/pregabalin
- Topical lidocaine, capsaicin
- Skeletal muscle relaxants: sedating, not evaluated well for chronic pain; avoid carisoprodol

Routinely integrate psychotherapeutic co-interventions
- Chronic pain often a complex biopsychosocial issue
- Opioids do not address psychosocial contributors to chronic pain; use as part of a multimodal treatment program
- Assess and treat for PTSD
- Cognitive-behavioral therapy, functional restoration, interdisciplinary therapy
- Motivational interviewing, relaxation techniques

Address sleep issues
- Avoid benzodiazepines
Patient selection and risk stratification for opioid therapies

- Risk assessment in all patients prior to initiating opioids
  - Aberrant drug-related behaviors occur in up to 50% of patients prescribed opioids for chronic non-cancer pain
  - Strongest predictor is personal or family history of alcohol or drug abuse; psychological comorbidities also a factor
  - Risk stratification can help guide the management plan

- Only consider opioids in patients in whom benefits likely to outweigh risks
  - Opioids are not always appropriate

- Tools for risk stratification are available
  - Accuracy for predicting future aberrant behaviors tend to be higher in initial studies and poorer/inconsistent in subsequent studies
Opioid Risk Tool (ORT)

**Administration**
- On initial visit
- Prior to opioid therapy

**Scoring**
- 0-3: low risk (6%)
- 4-7: moderate risk (28%)
- > 8: high risk (> 90%)

<table>
<thead>
<tr>
<th>Mark each box that applies</th>
<th>Female</th>
<th>Male</th>
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<tbody>
<tr>
<td>1. Family history of substance abuse</td>
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<tr>
<td>Alcohol</td>
<td>□ 1</td>
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<td>Illegal drugs</td>
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<td>Prescription drugs</td>
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<td>2. Personal history of substance abuse</td>
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<td>Alcohol</td>
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<td>Prescription drugs</td>
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<td>3. Age (mark if between 16-45 yrs)</td>
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<td>4. History of preadolescent sexual abuse</td>
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<td>5. Psychological disease</td>
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<tr>
<td>ADO, OCD, bipolar, schizophrenia</td>
<td>□ 2</td>
<td>□ 2</td>
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<tr>
<td>Depression</td>
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Scoring totals

Informed consent/chronic pain care plan

- Obtain informed consent prior to starting opioids
  - Counsel patient on potential adverse effects, risks associated to abuse potential
  - Some states require written documentation
- LOT management plans in all patients
  - Not a “contract”
  - Goals of therapy, how LOT will be prescribed and taken, expectations for follow-up and monitoring, alternatives to LOT, expectations regarding use of concomitant therapies, secure storage of opioids, and potential indications for tapering or discontinuing LOT
  - Some states require written management plan
Assess patients in multiple domains, prior to initiating therapy and periodically on therapy

- 4 A’s: analgesia, ADL’s, adverse events, aberrant behaviors
- Functional goals
  - Achievable, measurable
  - Function can improve even when pain is still present
- PEG scale—assess pain intensity and impact on function
- Screen for psychological comorbidities (PHQ-9, GAD, PHQ-4)
- Screen for substance abuse
  - AUDIT, CAGE, DAST
- PTSD screen: PCL-C
PEG Scale

1. What number best describes your pain on average in the past week:

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<th>9</th>
<th>10</th>
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<tbody>
<tr>
<td></td>
<td>No pain</td>
<td>Pain as bad as you can imagine</td>
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2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

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<tr>
<td></td>
<td>Does not interfere</td>
<td>Completely interferes</td>
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3. What number best describes how, during the past week, pain has interfered with your general activity?

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Krebs EE. JGIM 209;24:733-8
Initiation and titration of opioids

- View initial course of opioids as a short-term, therapeutic trial
  - The decision to proceed (or continue) with LOT should be a conscious one
  - Do not continue LOT in patients who are not benefitting
- Start at low doses and titrate cautiously
- Short- vs. long-acting opioids, round-the-clock versus PRN
  - No compelling evidence to routinely use RTC, long-acting opioids
    - Use of long-acting, RTC opioids based on cancer guidelines and expert opinion, potential benefits not proven for non-cancer pain; potential for tolerance, dose escalations, hyperalgesia
  - VA cohort study found initiation with long-acting opioid associated with higher risk of overdose than short-acting opioids (HR 2.33, 95% CI 1.26 to 4.32)
    - Risk highest in first 2 weeks after initiation
  - Buprenorphine for chronic pain in higher-risk patients?
• **Use methadone cautiously and understand pharmacology and risks**
  
• Increased methadone deaths nationwide
  * Methadone accounted for 1.7% of opioid rx’s in 2009 and 9.0% of morphine equivalents in 2010\(^a\)
  * Involved in 31% of opioid-related deaths, and 40% of single-drug deaths\(^a\)
  * Methadone associated with increased mortality risk vs. morphine in 1 cohort study but not another\(^b\)

• **Half-life 15 to 60 hours, up to 120 hours**
  * 60 hour half-life=12 days to steady-state
  * Start at 2.5 mg q8 hrs, increase slowly

• **Higher doses of methadone associated with greater QTc interval prolongation**
  * High proportion of torsades occurred on >200 mg/day
  * EKG monitoring, especially in persons with QTc risk factors

• **Morphine to methadone conversion ratio increases at higher doses**

• **Drug-drug interactions**

\(^a\)MMWR 2012;61:493-7;  
Time to reach steady state

Steady State
- Attained after approximately four half-times
- Time to steady state independent of dosage

CONCENTRATION

TIME (multiples of elimination half-time)
Prolonged QTc and torsades de pointes

A

B
Morphine to methadone conversion

<table>
<thead>
<tr>
<th>24 hour total oral morphine</th>
<th>Oral morphine to methadone conversion ratio</th>
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</thead>
<tbody>
<tr>
<td>&lt;30 mg</td>
<td>2:1</td>
</tr>
<tr>
<td>31-99 mg</td>
<td>4:1</td>
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<tr>
<td>100-299 mg</td>
<td>8:1</td>
</tr>
<tr>
<td>300-499 mg</td>
<td>12:1</td>
</tr>
<tr>
<td>500-999 mg</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1000 mg</td>
<td>20:1</td>
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</tbody>
</table>

Prescription drug monitoring programs

- Available now in almost all states
- Studies show that use of PDMPs can identify cases of diversion and doctor shopping
  - Co-prescribing with benzodiazepines decreased with use of a centralized prescribing system in Canada\(^a\)
  - Effects on clinical outcomes (e.g., overdose) not known
- Use of PDMPs variable and generally suboptimal
- PDMPs vary in who can access, information not available across states

\(^a\)Dormuth et al. CMAJ 2012
Urine drug tests

- Optimal frequency and usefulness of individualized vs. routine testing uncertain
  - Recommend checking prior to starting opioids and periodically
  - Risk may help guide testing intervals
- Urine drug tests can be difficult to interpret
  - Diagnostic accuracy for abuse/addiction difficult to determine
  - Need to understand metabolic pathways of different opioids
  - Differential diagnosis for abnormal results includes poorly controlled pain, drug abuse, diversion
  - Potential for false reassurance
  - No evidence that urine drug testing improves patient outcomes; potential for harms
  - Cost-effectiveness unclear
High-risk patients are more vulnerable to opioid abuse, misuse, addiction

Clinicians prescribing opioids in high-risk patients must be able to implement additional measures to manage these risks:

- More frequent monitoring
- Limited prescription fills
- Consultation with addiction specialists and mental health professionals
- Opioid-deterrent formulations?
- Naloxone?
Discontinuation of opioid therapy

• Taper or wean patients off of LOT when they:
  • Engage in intractable aberrant drug-related behaviors or drug abuse/diversion
  • Experience no progress towards meeting therapeutic goals
  • Experience intolerable adverse effects
• Continue to manage pain off opioids
• Have an exit strategy when starting LOT
  • Indications for stopping LOT
  • Plans for tapering or discontinuing
  • Opioid withdrawal not life-threatening
  • Clonidine for symptoms
  • May require prolonged taper
  • Resources for managing addiction and mental health issues
Case

- Patient initially transferred care in 2008
- Unclear if benefitting from very high doses of long-term opioid therapy, worsening of GI symptoms; no signs of aberrant behaviors
- Slow taper initiated
  - Morphine 450 mg/day → 120 mg/day
  - Oxycodone 160 mg/day → 5 mg po bid prn
    - 690 mg MED/day → 135 mg/day
- Added non-opioid medications
  - Duloxetine 20 mg qD
  - Buspirone 30 mg bid
- Pain and function no worse than when on high doses, no serious withdrawal
  - Goal is to get down to <100-120 mg MED/day
Conclusions

• Data on long-term benefits sparse; opioids may have little effect on (or worsen) functional outcomes
• Dose-dependent risks of opioids, with limited evidence on benefits of higher doses
• No opioid is “safe”
• Taken together, the available evidence suggests that potential benefits of opioids are at best finely balanced with harms
  • More selective and cautious prescribing of opioids indicated, particularly with higher doses
  • Use non-opioid treatments for chronic pain, particularly those addressing psychosocial factors
  • Avoid higher doses
  • Need to assess risk as standard practice
  • Routine integration of risk mitigation strategies in clinical practice based on level of assessed risk
  • Identify and avoid high-risk prescribing practices
  • Focus on function, rather than just pain
  • Policy efforts needed to facilitate use of non-opioid alternatives and implement risk mitigation strategies
PCSS-O Colleague Support Program and Listserv

- PCSS-O Colleague Support Program is designed to offer general information to health professionals seeking guidance in their clinical practice in prescribing opioid medications.
- PCSS-O Mentors comprise a national network of trained providers with expertise in addiction medicine/psychiatry and pain management.
- Our mentoring approach allows every mentor/mentee relationship to be unique and catered to the specific needs of both parties.
- The mentoring program is available at no cost to providers.

For more information on requesting or becoming a mentor visit: www.pcss-o.org/colleague-support

- Listserv: A resource that provides an “Expert of the Month” who will answer questions about educational content that has been presented through PCSS-O project. To join email: pcss-o@aaap.org.
PCSS-O is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with: Addiction Technology Transfer Center (ATTC), American Academy of Neurology (AAN), American Academy of Pain Medicine (AAPM), American Academy of Pediatrics (AAP), American College of Physicians (ACP), American Dental Association (ADA), American Medical Association (AMA), American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA), American Society for Pain Management Nursing (ASPMN), International Nurses Society on Addictions (IntNSA), and Southeast Consortium for Substance Abuse Training (SECSAT).

For more information visit: www.pcss-o.org
For questions email: pcss-o@aaap.org

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