Opioid Therapy For Pain: An Evidence Review

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Education

Educational Objectives

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

- Review evidence on use of opioid therapy for chronic pain
- Assess risks and benefits of long-term opioid therapy for chronic pain and factors associated with prescription opioid overdose and abuse

**Note:** Best practices to reduce risks related to prescription opioids are discussed in a different lecture
Case

• 53-year old female transferring care because her PCP is leaving practice
  - Shoulder and hip pain secondary to avascular necrosis, s/p shoulder replacements, hip decompression, hip replacement
  - Fibromyalgia, non-radiculor low back pain, chronic headache
  - Depression, fatigue
  - Gastroparesis, irritable bowel syndrome
  - Morphine IR 30 mg 5 tabs (150 mg) every 8 hrs + oxycodone 5 mg 8 tabs (40 mg) every 6 hrs
    - MED/day: 690 mg
  - Modafinil 20 mg po daily
  - Pain 6/10 on average, with day to day fluctuation
  - Can carry out activities of daily living with pain, limited exercise, no aberrant behaviors
Background

- Chronic non-cancer pain highly prevalent, with substantial burdens
  - Estimates vary, up to 1/3 of adults report some CNCP
- Opioids are increasingly prescribed for chronic non-cancer pain
  - About 5% of adults report use of long-term opioid therapy (LOT)\textsuperscript{a}
  - The U.S. is \textasciitilde 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
- Large practice variations in use of LOT

\textsuperscript{a}Boudreau et al Pharmacoepidemiol Drug Saf 2009
CDC: Parallel increases in opioid sales, deaths and substance abuse

US opioid sales quadrupled 2000-2010

Since 2008, 15,000 deaths per year. This exceeds MVA deaths in 30 states.

Risk of Prescription Opioid Overdose by Age, 2008

Rates are per 100,000 population age-adjusted to 2008 U.S. standard population

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm
Opioid prescriptions per person by age group, U.S., 2009

Source: Volkow et al. JAMA 2011;305:1299-1301

Nonmedical Pain Medication Use Among Adolescents and Young Adults
First Opioid of Abuse in Those Using Heroin

![Graph showing the percentage of total sample using prescription opioids and heroin over decades.](image-url)
Prescribing Trends

- Opioid use for chronic pain increased from 8% to 16%
  - Use of more potent opioids increased from 2 to 9%
  - Increases observed across age groups and in men and women
  - Increased use of schedule II opioids; greatest increase in daily doses occurred in prescriptions of schedule II opioids

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.”
    Portenoy RK. J Law Medicine Ethics 1996;24:296
- 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.”— Portenoy RK. J Pain Symptom Management 1996;11:203
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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\(^a\)
  - Opioids more effective than placebo for nociceptive and neuropathic pain (effects moderate; effect sizes 0.55-0.60)
  - Maximum dose ≤180 MME/day in all trials except for 3

- **Long-term effectiveness**
  - Cochrane review included 26 studies >6 months\(^b\)
  - No placebo-controlled trials
  - 25 studies were case series or uncontrolled long-term trial continuations
  - Many discontinuations due to adverse effects (23%) or insufficient pain relief (10%), but some patients who continued on opioids experienced long-term pain relief

\(^a\)Furlan et al. Pain Res Manag 2011
\(^b\)Noble et al. Cochrane Database Syst Rev 2010
Limitations of Evidence on Effectiveness of LOT

- Effects on function generally smaller than effects on pain; some trials show 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 compared LOT vs. cognitive behavioral-based exercise therapy or interdisciplinary rehabilitation
Abuse, Addiction, Misuse

- Estimates vary from 4% to 26%, or higher
  - One study (n=801) based on standardized interviews\(^a\)
    - 26% purposeful oversedation
    - 39% increased dose without prescription
    - 8% obtained extra opioids from other doctors
    - 18% used for purposes other than pain
    - 12% hoarded pain medications
  - Definitions inconsistent across studies and behaviors evaluated vary in seriousness
  - Poorly standardized methods to detect these outcomes
  - Data from efficacy trials underestimate risks

\(^a\)Fleming et al. J Pain 2007
Factors associated with increased risk of overdose, or observed in high proportions of overdoses

- Aberrant behaviors
  - Obtaining opioid prescriptions from multiple providers
- Recent initiation of opioids
- Methadone
- Concomitant use of benzodiazepines
- Substance abuse
- Psychological comorbidities
- Higher doses of opioids
Overdose: Dose-response Relationship

- 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.
  - Potential for residual confounding by indication.
- Difficult to determine whether patients had chronic pain and duration of therapy.
Association Between Opioid Dose and Overdose Risk

- **Cohort study (n=9940, 51 opioid overdoses, 6 fatal)**
  - Risk of opioid overdose (vs. 1 to <20 mg/day)
    - >=100 mg/d: HR 8.9 (4.0-20)
    - 50-<100 mg/d: HR 3.7 (1.5-9.5)
    - 20-<50 mg/d: HR 1.4 (0.57-3.6)

- **Case-control study (VA, 750 cases)**
  - Risk of opioid overdose-related death (vs. 1 to <20 mg/day)
    - >=100 mg/d: HR 7.2 (4.8-11)
    - 50-<100 mg/d: HR 4.6 (3.2-6.7)
    - 20-<50 mg/d: HR 1.9 (1.3-2.7)

- **Nested case-control study (Ontario, 498 cases)**
  - Risk of opioid-related mortality (vs. 1 to <20 mg/day)
    - >=200 mg/d: OR 2.9 (1.8-4.6)
    - 100-199 mg/d: OR 2.0 (1.3-3.2)
    - 50-99 mg/d: OR 1.9 (1.3-2.8)
    - 20-49 mg/d: OR 1.3 (0.94-1.8)

Other Harms of Opioids

- High rates of adverse events
  - Constipation, nausea, sedation, and others
- Hyperalgesia
  - Paradoxical increased sensitivity to pain
  - Prevalence, risk factors and clinical significance not well understood
- Hypogonadism
  - Primarily based on cross-sectional studies
  - One study showing association with increased use of testosterone and ED meds
- Falls/fracture risk
- Myocardial infarction
- Poorer functional outcomes
  - One study of patients in WA state workers’ compensation system with low back injury found increased risk of disability at 1 year in patients who received opioids within 6 weeks (adjusted OR 2.2, 95% 1.5 to 3.1)

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\(^a\)Deyo 2013
\(^b\)Franklin et al. Spine 2008
Initiation and Titration of Opioids

- Initial course of opioids should be viewed 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
  - Re-assess within 1-4 weeks
- Start at low doses and titrate cautiously
- Insufficient evidence to recommend short- vs. long-acting opioids, round-the-clock versus PRN
  - Practice of long-acting, round-the-clock dosing based on cancer guidelines and expert opinion, potential benefits not proven
  - Potential harms of long-acting, round-the-clock opioids include development of hyperalgesia, tolerance, endocrinologic adverse effects
  - Initiation with long-acting opioids associated with increased risk of overdose (Miller et al. JAMA Intern Med 2015;175:608)
  - Methadone and fentanyl not recommended as first line options due to less predictable/more complicated dosing/pharmacokinetics
  - Buprenorphine for chronic pain in higher risk patients; evidence lacking to show improved safety but theoretically lower respiratory risk
Methadone

- Synthetic opioid used for treatment of addiction and pain
- Increased methadone deaths nationwide
  - 1999: 800 deaths → 2008: 4900 deaths
  - 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\(^a\)
- 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 reported cases of torsades de pointes occurred in patients prescribed >200 mg/day
  - ECG monitoring at baseline and at higher doses\(^b\)
- Morphine to methadone conversion ratio increases at higher doses

\(^a\)MMWR 2012;61:493-7  
\(^b\)Chou R J Pain 2014;15:321-37
Time to Reach Steady State

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

Steady State Concentrations

http://www.rxkinetics.com/pktutorial/1_6.html
Prolonged QTc and Torsades de Pointes

Figure 1 – Admitting ECG shows normal sinus rhythm with atrial bigeminy, nonspecific T-wave abnormality, and QTc prolongation (626 msec).

Figure 2 – Rhythm strip shows TdP.

# Morphine to Methadone Conversion

<table>
<thead>
<tr>
<th>24 hour total oral morphine</th>
<th>Oral morphine to methadone conversion ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 mg</td>
<td>2:1</td>
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<tr>
<td>31-99 mg</td>
<td>4:1</td>
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<tr>
<td>100-299 mg</td>
<td>8:1</td>
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<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>
</tr>
</tbody>
</table>

Fentanyl

- Absorption and pharmacodynamics of transdermal fentanyl are complex
- Gradually increasing serum concentration during the first part of the 72-hour dosing interval
- Variable absorption based on factors such as external heat
- Dosing in mcg/hr instead of mg
- Should be prescribed with clinicians familiar with its use and complexities
Dosing

- No theoretical ceiling with opioids
  - But, little evidence to guide prescribing at higher doses
  - Additional risks (hyperalgesia, endocrine), unclear benefit, and can be a marker for abuse, addiction, or diversion
  - Higher doses associated with increased risk of overdose
  - Unclear if persons who don’t respond at relatively low doses will respond at higher doses (opioid non-responders)
- Definitions of “higher dose” have varied and continue to evolve; trend towards lower dose thresholds based on new evidence on dose-dependent overdose risks
  - 2009 APS/AAPM guideline defined >200 MME/day of as “higher dose”
  - 2016 CDC guideline recommends caution at 50-90 MME/day and to avoid doses >90 MME/day
- Mitigating risks of higher doses
  - 2009 APS/AAPM guideline defined >200 MME/day of as “higher dose”
  - Counsel patients on risks and provide opportunity to taper
  - More frequent or intense monitoring
  - Consider tapering off medication if not achieving therapeutic goals
  - Consider providing Naloxone in conjunction with overdose education
  - Avoid co-prescribing of benzodiazepines and other medications that may increase risk
High-dose Opioid Therapy Prescribing Patterns

• Small proportion of patients account for the majority of opioids prescribed
  ▪ In one study, 5% of opioid users accounted for 48% to 70% of total use

• Factors associated with high dose therapy include:
  ▪ Presence of substance use disorders
  ▪ Presence of mental health disorders
  ▪ Use of sedative-hypnotics and multiple opioids
  ▪ Higher health service utilization
  ▪ Multiple pain problems and high levels of medical and psychiatric comorbidity

• “Adverse selection”— persons at highest risk are most likely to receive high dose opioids
  ▪ Increasing the opioid dose should not be the main response in patients with important psychosocial risk factors or high distress

Effects of Dose Threshold Policies

- In 2007, WA state implemented dosing policy of <120 mg/day morphine equivalents in workers’ compensation
  - After 2007, proportion prescribed >120 mg/day decreased by 35%
  - 50% decrease from 2009 to 2010 in number of opioid-related deaths; trend so far sustained
  - Data observational, subject to confounding and attribution bias

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Mitigating Risks Associated with Opioids

- Avoid higher doses
- Monitoring, including urine drug testing
  - Reassess at least every 3 months, more frequently for higher-risk persons, after initiation and dose increases
- Review 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?
Urine Drug Tests

• Recommended to help identify risky behaviors that would otherwise be undisclosed
  ▪ Non-invasive, objective documentation of compliance with treatment plan, including use or absence of prescribed drugs, non-prescribed drugs, and illicit substances
  ▪ Longer window or detection compared to blood

• When to perform urine drug testing
  ▪ At baseline and periodically, interval may be guided in part by assessed risk
    • Test if suspected aberrant behaviors and after major changes in treatment
  ▪ Optimal frequency and usefulness of individualized or random vs. routine testing uncertain
    • 1-2 times/year may be appropriate for low-risk patients; 3-4 or more times per year for higher risk
    • Individualized or random testing may miss some abnormal tests, but higher yield and reduced costs
    • Patients may have more opportunity to tamper or alter behavior if testing expected
Marijuana Use and Opioids

- High prevalence of marijuana use in patients with chronic pain, with or without opioids
  - 6.2% to 39% (Reisfield et al. Pain Med 2009;10:1431)
- Marijuana may have analgesic effects, particularly for neuropathic pain
  - Effects of marijuana vary depending on THC vs. cannabidiol (CBD) content
    - THC associated with psychoactive/intoxicating effects
    - CBD associated with medicinal effects
- Some evidence that marijuana may be associated with decreased opioid doses
- Little evidence on psychomotor and other effects in patients using marijuana and opioids
- Association between marijuana use and opioid and other substance misuse
- Increased risk of MVA with marijuana
- Caution in patients unable to decrease marijuana use
Opioid-deterrent Formulations

- Opioid-deterrent formulations recently approved by FDA or undergoing FDA approval process
  - Designed to be tamper-resistant or co-formulated with medications that reverse opioid effects or produce noxious side effects when tampered with
  - Effectiveness for reducing misuse/substance abuse and improving clinical outcomes yet to be established
  - Likely to be primarily effective in patients who crush or inject opioids
  - Some patients may seek other prescription or illicit opioids

*Cicero et al. NEJM 2012*
High-risk Patients

- 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
    - Medication assisted treatment (use of methadone, buprenorphine, or naltrexone in conjunction with psychological therapies) recommended for most patients with opioid use disorder
  - Opioid-deterrent formulations may be helpful
  - Consider naloxone
Evaluation of Aberrant Drug-related Behaviors

• Aberrant drug-related behaviors must be evaluated
  ▪ Behaviors vary in seriousness
  ▪ Need to judge seriousness, the cause or causes, likelihood of recurrence, and clinical context
    – Predictors of high likelihood of future aberrant behaviors include 3 or more episodes of aberrant behaviors and sense of “losing control”
    – Serious behaviors include diversion, injecting oral drugs
  ▪ Responses range from patient education and enhanced monitoring to referral to addiction specialist and discontinuation of therapy
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 initiating a trial of LOT**
  - Indications for stopping LOT
  - Plans for tapering or discontinuing
    - Reduction in daily dose of 10% per week reasonable starting point
  - Some patients may require slower tapers
  - Know resources for managing addiction and mental health issues
Driving and Work Safety

• Opioids may cause somnolence, incoordination, clouded mentation, or slower reflexes
• Counsel patients not to drive or perform dangerous activities when impaired
  ▪ Impairment more likely when starting therapy, when increasing doses, and when using other drugs with psychoactive effects
  ▪ No evidence that patients on opioids should be restricted from driving in the absence of signs of impairment
  ▪ State laws vary on reporting requirements
Use of Opioids for Acute Pain

- Opioids generally considered the most effective medication for acute pain
  - But, recent data indicates that opioids may be no more effective than an NSAID alone for acute pain
    - In LBP adding oxycodone/acetaminophen to an NSAID did not improve pain or function at 1 week (Friedman BW. JAMA 2015;314:1572)
- Use of opioids for “minor” pain associated with increased risk of long-term use
  - Versus no opioid use, opioid within 7 days of minor surgery associated with 44% increased risk of use at 1 year (Alam A. Arch Intern Med 2012;172:425)
- Prescribing excessive quantities of opioids for acute pain resulting in leftover opioids
  - Source of diversion and unprescribed use
- More judicious use of opioids for acute pain
  - If used, limit opioids to a 3-5 day supply for most acute pain
Conclusions: What is the evidence?

- Very limited data on long-term benefits of high dose opioid therapy
- Accumulating evidence on serious harms of long-term opioid therapy that appear to be dose-dependent
- Benefits appear limited and harms are significant, suggesting at best a close balance of benefits to harm
- Titrating to achieve pain relief is inconsistent with data on opioid benefits
- Special caution with methadone
- No clear advantage to long-acting, RTC prescribing
- A number of risk factors for overdose have been identified
- Patients on high doses warrant re-evaluation, additional monitoring, and follow-up
- Decrease dose or discontinue in patients who are not improving
Case

- Unclear if benefiting from very high doses of long-term opioid therapy, ?worsening of GI symptoms
- No signs of aberrant behaviors
- Slow taper initiated, over ~2 years
  - Morphine 450 mg/day → 120 mg/day
  - Oxycodone 160 mg/day → 5 mg bid prn
    - 690 mg/MED/day → 135 mg/day
- Added non-opioid medications
  - Duloxetine 30 mg qD
  - Buspirone 30 mg bid
- Pain and function no worse than when on high doses, no serious withdrawal
  - Some periods of acute pain with temporary increases in opioids
- Goal is to get down to <100 to 120 mg MED/day
Evidence-informed Approach to Appropriate Use of Opioids

- Preference for non-opioid therapies
  - Opioid alone do not address the psychosocial contributors to chronic pain
- Not all patients are appropriate for opioid therapy
- Use risk assessment to inform decisions
- Initiate at low doses and titrate slowly
- View initial treatment as a therapeutic trial
- Routine monitoring and risk mitigation
- Titration should be based on responsiveness of patients to low doses
  - Patients who do not respond to low doses probably will not respond to higher doses—“opioid non-responders”
  - Taper in patients not responding or experiencing adverse effects
- Caution when reaching threshold doses
  - Optimal dose threshold uncertain
  - Much easier to titrate up doses than to titrate down
References

References

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](http://www.pcss-o.org)
For questions email: pcss-o@aaap.org

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