Opioids for Chronic Pain: Evidence, Clinical Practice, and Policy

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Conflict of interest disclosure

Dr. Chou has received research funding from the Agency for Healthcare Research and Quality, the American Pain Society, and the Centers for Disease Control and Prevention
Session Objectives

- Understand opioid prescribing patterns and epidemiology
- Understand risks and benefits of long-term opioid therapy for chronic pain
- Identify recommendations for safer opioid prescribing based on clinical practice guidelines, and understand implications for clinical practice

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
  - 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

*Boudreau et al Pharmacoepidemiol Drug Saf 2009
Since 2008, 15,000 deaths per year. This exceeds MVA deaths in 30 states.

US opioid sales quadrupled 2000-2010

Nonmedical pain medication use among adolescents and young adults

SAMSHA 2010 National Survey on Drug Use and Health
Recent Opioid Overdose Trends

**Opioid Overdose Trends, 2000-2013**

![Graph showing opioid overdose trends from 2000 to 2013, with a significant increase in deaths per 10,000 population for both prescription opioids and heroin.](image1)

Source: CDC/NCHS National Vital Statistics System NCHS Data Brief, No. 190, March 2015

First opioid of abuse in heroin users

![Graph showing the percentage of people using prescription opioids and heroin as their first opioid, with a decline in prescription opioids and an increase in heroin use from the 1960s to the 2010s.](image2)

Gioaro TJ et al. JAMA Psychiatry 2014
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.” —Inturrisi C. Clin J Pain 2002;18:S3-13
  - No theoretical dose ceiling

Dose-response relationship for respiratory depression

Dahan A. Br J Anaesth 2005;94:825-34
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
- Observational studies describing benefits of opioid therapy for non-cancer pain, with low rates of abuse, addiction, or other serious AE’s
  - Case series, hospitalized patients, most on low doses
- 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
- Emphasis on round-the-clock dosing using sustained-release formulations
  

“The risk of addiction is much less than 1%”


ADDITION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 19,946 hospitalized medical patients who were monitored consecutively. Although there were 11,863 patients who received at least one narcotic prescription, none was identified as having evidence of narcotic addiction. None of the patients who had a history of addiction had received a narcotic prescription either before or after their hospitalization. It is estimated that 1.5% to 2% of patients addicted to narcotic drugs are hospitalized in any year; these patients are more likely to be addicted to heroin. In our study, we could not identify any evidence of addiction in patients who had no history of addiction. The addiction was contingent on the initial use of heroin. The drugs prescribed were inappropriate in two patients. Percodan in one, and intravenous in the other. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

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Cited 824 times (Google Scholar)
Background for CDC guideline

- Need to address prescription opioid prescribing as a public health problem given marked increases in overdoses and OUD
- Guidelines developed by several states and agencies but have inconsistencies in methods and recommendations
- National guidelines don’t incorporate the most recent evidence
- Clinicians report uncertainty about how to prescribe opioids and want clear, consistent guidance
- Primary audience: Primary care providers
- Target population: Adults with chronic pain
  - Exclude: Patients undergoing active treatment for cancer, palliative care, end-of-life care

Guideline Development Process

- Analyze
  - Systematic Literature Review
  - CDC Draft Recommendations
  - Core Expert Group Consultation
  - CDC Draft Guideline

- Consult
  - Core Expert & Stakeholder Review
  - Federal Partner Review
  - Peer Review
  - Constituent Input (Webinar)

- Comment
  - CDC Revised Guideline
  - FRN Public Comment
  - Federal Advisory Committee Review
  - Publication of Guideline (March 19, 2016)

- Review
Clinical Evidence Review

- 2014 AHRQ-sponsored review for NIH Pathways To Prevention Workshop
- CDC commissioned review update in 2015
- Key questions addressed:
  - Effectiveness and comparative effectiveness
  - Harms/adverse events
  - Dosing strategies
  - Risk mitigation strategies
  - Effects of opioid use for acute pain on long-term use

Systematic Review Findings

- No long-term (≥1 year) outcomes in pain/function
  - Most placebo-controlled trials ≤6 weeks; effects small-moderate for pain, limited for function
- Opioid dependence in primary care: 3% to 26%
- Dose-dependent association with risk of overdose/harms
  - No evidence that dose escalations associated with improved pain/function
- No clear differences between round-the-clock and/or long-acting vs. PRN and/or immediate-release
  - Initiation with long-acting opioid associated with increased risk of overdose
- Methadone and concomitant use of benzodiazepines associated with higher mortality/overdose risk
- Accuracy of risk prediction instruments inconsistent and suboptimal
- Increased likelihood of long-term use when opioids used for acute pain
Organization of recommendations

- 12 recommendations grouped into three conceptual areas:
  - When to initiate or continue opioids for chronic pain (1-3)
  - Opioid selection, dosage, duration, follow-up, and discontinuation (4-7)
  - Assessing and mitigating harms of opioid use (8-12)
- Recommendations graded as category A (strong) or B (conditional)
- Supporting evidence type classified as 1 (well-conducted RCT's) through 4 (observational studies with limitations)

Recommendation #1

- Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain.
- Consider opioid therapy only if expected benefits are anticipated to outweigh risks to the patient.
- If opioids are used, combine with appropriate nonpharmacologic therapy and nonopioid pharmacologic therapy.

(Recommendation category A: Evidence type: 3)
Opioids are not first-line or routine therapy for chronic pain

- A number of nonopioid therapies are effective for chronic pain
  - Benefits similar or slightly less than opioids, with substantially lower risk of serious harms
  - Consider “active” therapies such as exercise or cognitive behavioral therapy (CBT) that address psychosocial contributors and focus on movement/function
  - Consider pharmacologic therapy (NSAIDs, acetaminophen, anticonvulsants, SNRIs) in conjunction with nonpharmacologic therapy

- When opioids used, combine with nonopioid therapies to provide greater benefits.
  - Biopsychosocial approach to chronic pain
  - Address psychological comorbidities

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 inconsistent and poor in some 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%)

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Scoring totals

Recommendation #2

- Before starting opioid therapy for chronic pain, establish treatment goals with all patients, including realistic goals for pain and function, and have a plan for discontinuation of therapy if benefits do not outweigh risks.
- Continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.

(Recommendation category A: Evidence type: 4)

Establish and measure progress towards goals

- Before initiating opioid therapy for chronic pain
  - Be explicit about expected benefits.
  - Determine how effectiveness will be evaluated.
  - Establish realistic treatment goals with patients.
  - Focus on improvement in function as well as pain

- 3-item PEG Assessment Scale*
  - Pain average (0-10)
  - Interference with Enjoyment of life (0-10)
  - Interference with General activity (0-10)

*30% = clinically meaningful improvement
Recommendation #3

Before starting and periodically during opioid therapy, discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

(Recommendation category A: Evidence type: 3)

Ensure patients are aware of harms associated with opioids

• Discuss:
  ○ serious and common adverse effects
  ○ increased risks of overdose
    ❖ at higher dosages
    ❖ when opioids are taken with other drugs or alcohol
  ○ periodic reassessment, PDMP and urine checks; and
  ○ risks to family members and individuals in the community.
Recommendation #4

- When starting opioid therapy for chronic pain, prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.

(Recommendation category A: Evidence type: 4)

Dosing strategies and selection of opioids

- Initiate therapy with short-acting opioids
- Caution with use of methadone
  - Not first-line ER/LA opioid
  - Must be familiar with unique risks and be prepared to educate and closely monitor patients when prescribing for pain.
  - Long/unpredictable half-life, QTc prolongation, incomplete cross-tolerance (high morphine:methadone dose conversion ratios at higher doses)
- Caution with transdermal fentanyl
  - Complicated dosing and absorption properties
Time to reach steady state

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

Prolonged QTc and torsades de pointes
Recommendation #5

- When opioids are started, prescribe the lowest effective dosage.
- Use caution when prescribing opioids at any dosage
  - Reassess when increasing dosage to \( \geq 50 \) morphine milligram equivalents (MME)/day
  - Avoid increasing dosage to \( \geq 90 \) MME/day

(Recommendation category A: Evidence type: 3)
Dose considerations

- Start at low dose and increase gradually by smallest practical amount.
  - In VA study, average dose in overdoses 98 MME/day
  - ~50% of overdoses occurred in patients prescribed <60 MME/day.
- If total opioid dosage ≥50 MME/day
  - reassess pain, function, and treatment
  - increase frequency of follow-up; and
  - consider naloxone.
- Avoid increasing opioid dosages ≥90 MME/day.
  - only consider in patients with incremental benefits relative to harms.
- If escalating dosage requirements
  - discuss other pain therapies with the patient
  - consider working with the patient to taper opioids down or off
  - consider consulting a pain specialist.

Tapering Opioids

- Work with patients to taper opioids down or off when
  - no sustained clinically meaningful improvement in pain and function
  - opioid dosages ≥50 MME/day without evidence of benefit
  - concurrent benzodiazepines can’t be tapered off
  - patients request dosage reduction or discontinuation
  - patients experience overdose, other serious adverse events, warning signs.
- Taper slowly enough to minimize opioid withdrawal
  - A decrease of 10% per week is a reasonable starting point; some (many) patients may require slower taper
- Optimize nonopioid pain management and psychosocial support
If patient is already receiving a high dosage

- For established patients already taking \( \geq 90 \) MME/day who otherwise do not meet criteria for tapering:
  - Discuss recent evidence regarding dose-dependent overdose risk
  - Re-evaluate continued use of high opioid dosages
  - Offer opportunity to taper

- For patients who agree to taper opioids to lower dosages, collaborate with the patient on a tapering plan.

Recommendation #6

- When opioids are used for acute pain, prescribe the lowest effective dose of immediate-release opioids and prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.
  - 3 days or less will often be sufficient; more than 7 days rarely needed.

(Recommendation category A: Evidence type: 4)
**Opioids and acute pain**

- Prescribe the lowest effective dose.
- Prescribe amount to match the expected duration of pain severe enough to require opioids.
- Often ≤ 3 days and rarely more than 7 days needed.
- Do not prescribe additional opioids “just in case”.
- Re-evaluate patients with severe acute pain that continues longer than the expected duration to confirm or revise the initial diagnosis and to adjust management accordingly.
- Do not prescribe ER/LA opioids for acute pain treatment.

**Recommendation #7**

- Evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation.
- Evaluate benefits and harms of continued therapy every 3 months or more frequently.
- If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

(Recommendation category A: Evidence type: 4)
Follow-up

- At follow up, determine whether
  - opioids continue to meet treatment goals
  - there are common or serious adverse events or early warning signs
  - benefits of opioids continue to outweigh risks
  - opioid dosage can be reduced or opioids can be discontinued.

Recommendation #8

- Before starting and periodically during continuation of opioid therapy, evaluate risk factors for opioid-related harms.
- Incorporate into the management plan strategies to mitigate risk
  - Consider naloxone when factors that increase risk for opioid overdose are present; e.g. history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use

(Recommendation category A: Evidence type: 4)
**Recommendation #9**

- Review the patient’s history of controlled substance prescriptions using state PDMP data.
- Monitor PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy, ranging from every prescription to every 3 months.

(Recommendation category A: Evidence type: 4)

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**If prescriptions from multiple sources, high dosages, or dangerous combinations**

- Discuss safety concerns with patient (and any other prescribers they may have), including increased risk for overdose.
- For patients receiving high total opioid dosages, consider tapering to a safer dosage, consider naloxone.
- Assess for opioid use disorder.
- Do not dismiss patients from care—use the opportunity to provide potentially lifesaving information and interventions.
Recommendation #10

- Obtain urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.

(Recommendation category B: Evidence type: 4)

Use UDT to assess for prescribed opioids and other drugs that increase risk

- Be familiar with urine drug testing panels and how to interpret results.
- Before ordering urine drug testing
  - explain to patients that testing is intended to improve their safety
  - explain expected results; and
  - ask patients whether there might be unexpected results.
- Discuss unexpected results with local lab and patients.
- Verify unexpected, unexplained results using specific test.
- Do not dismiss patients from care based on a urine drug test result.
Recommendation #11

- Avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.

(Recommendation category A: Evidence type: 3)

Avoid concurrent opioids and benzodiazepines whenever possible

- Concomitant benzodiazepine use observed in a high proportion of opioid-related overdose deaths.
  - other medications with respiratory depressant effects may also be associated with similar risks
- Taper benzodiazepines gradually.
- Offer evidence-based psychotherapies for anxiety.
  - cognitive behavioral therapy
  - specific anti-depressants approved for anxiety
  - other non-benzodiazepine medications approved for anxiety
- Coordinate care with mental health professionals.
Recommendation #12

- Offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

(Recommendation category A: Evidence type: 2)

If you suspect opioid use disorder (OUD)

- Discuss with your patient and provide an opportunity to disclose concerns.
- Assess for OUD using DSM-5 criteria. If present, offer or arrange MAT.
  - Buprenorphine through an office-based buprenorphine treatment provider or an opioid treatment program specialist
  - Methadone maintenance therapy from an opioid treatment program specialist
  - Oral or long-acting injectable formulations of naltrexone (for highly motivated non-pregnant adults)
- Consider obtaining a waiver to prescribe buprenorphine for OUD (see http://www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management)
Mitigating risks associated with use of opioids

- Use lower doses
- Don’t initiate with long-acting opioids
- More frequent follow-up
- Monitoring, including urine drug testing and PDMP monitoring
- Avoid sedative-hypnotics (particularly benzodiazepines)
- Diagnose and treat OUD
- Addiction, pain, or psychiatric consultation
- More frequent refills with smaller quantities
- Abuse-deterrent formulations
- Naloxone co-prescription

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”
- The available evidence suggests that potential benefits of opioids are at best finely balanced with harms, supporting the approach in the CDC guideline
  - More selective and cautious prescribing of opioids indicated
  - Use non-opioid treatments, particularly those addressing psychosocial factors
    - Prioritize more “active” versus less active therapies?
  - Avoid higher doses
  - Assess risk as standard practice
  - Routinely integrate risk mitigation strategies
  - 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
References/Resources

- CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016
  - MMWR 2016;65:1-49
  - JAMA 2016;315:1624-45
- Slide set summarizing CDC guideline
- Fact sheets, checklists, dose calculators
  - [http://www.cdc.gov/drugoverdose/prescribing/resources.html](http://www.cdc.gov/drugoverdose/prescribing/resources.html)