



Topic Brief: Long-Term Opioid Treatment for Chronic Pain

June 9, 2015

High-Level Research Question

What is the comparative effectiveness and risks of long-term opioid use for the management of chronic pain?

Assignment for Workgroup Participants

- Based on your perspective (patient, clinician, payer, etc.), what are two or three of the most relevant comparative effectiveness research (CER) questions on the use of long-term opioid therapy for chronic pain that warrant further research?
- Submitted questions will be used to generate the agenda for the workgroup meeting.

This document was prepared for informational purposes only and should not be construed as medical advice or used for clinical decision making.

Opportunity Snapshot

As part of PCORI's efforts to fund high-impact and useful research on critical patient-centered health and healthcare issues, PCORI is hosting a multistakeholder workgroup to discuss high-priority topics that focus on the comparative effectiveness of long-term opioid use for the treatment of chronic pain. PCORI intends to use feedback from the workgroup to conduct further gap analyses and to develop a funding announcement in this area. The objective of the workgroup is to create a set of comparative research questions whose findings could improve patient-centered outcomes.

1. Overview

Chronic pain is highly prevalent and a leading cause of disability and decreased quality of life (1–2). Opioids are widely accepted for the treatment of cancer-related chronic pain in the palliative care setting; however, their use for other types of chronic pain remains controversial (3). For the purpose of this topic brief, chronic pain is defined as pain lasting longer than three months or past the time of normal healing (4). Despite the stark absence of high-quality evidence to demonstrate the safety and effectiveness of long-term opioid therapy for the management of chronic pain, the use of prescription opioid therapy is rising (4). Over the last 20 years, opioid prescriptions have increased by 300 percent, with an estimated 201.5 million dispensed in 2009 (5–7). In addition, an increasing number of emergency room visits, hospitalizations, and deaths have been linked to opioid overdoses (8). Researchers suggest that the opioid crisis may be due, in part, to several factors, including: 1) opioid use was once largely discouraged but is now included in the standards of care; 2) the public appears to believe that prescription opioids are safer to abuse than illicit drugs; and 3) common drug-drug and drug-disease interactions may contribute to the increase in overdoses (8, 9–14).

In tandem with the rapid uptake of pharmacologic therapies for chronic pain are national efforts to reduce the use of opioids and the incidences of prescription-related death and dependence. For example, the Department of Veteran Affairs (VA) launched the Opioid Safety Initiative in 2013, which emphasizes patient education, close patient monitoring, and the use of such complementary and alternative practices as acupuncture and behavior therapy in lieu of habit-forming opiates. The US Department of Health and Human Services (HHS) recently announced a targeted initiative to reduce prescription opioid- and heroin-related overdoses, death, and dependence through training/education resources for health professionals; increased use of naloxone; and the use of medication-assisted treatment.

Given the current opioid crisis, the question remains: "Are we as a nation approaching the management of chronic pain in the best possible manner that maximizes effectiveness and minimizes harm" (15)? A balanced approach—one that recognizes patients' legitimate medical needs for opioids and acknowledges the potential serious harms of misuse, abuse, and addiction—will be needed (3).

2. Patient Centeredness

Chronic pain research that evaluates important patient-centered outcomes—such as pain management, functionality, safety, and quality of life—are greatly needed and relevant to patients, their caregivers, clinicians, and other key stakeholders.

3. Burden of Disease

The Institute of Medicine estimates that more than 100 million Americans—approximately one-third of the US population—suffer from chronic pain. The societal costs of pain top \$560 billion per year from medical expenses, disability, and lost wages and productivity (16). Despite various treatment options for pain, between 5 million and 8 million Americans

use opioids for chronic pain management (16). Mounting evidence suggests that opioids may be associated with important harms including overdose, abuse, addiction, and diversion (17–23). From 2001 to 2013, there was a three-fold increase in the total number of deaths from prescription opioids; in 2010, there were more than 600,000 emergency department visits due to opioid misuse and abuse (20, 24). Other common adverse events from opioid therapy include sedation, impaired cognitive function, depression, constipation, and bladder dysfunction (6, 25).

4. Ongoing Evidence Gaps

This section briefly summarizes information from recently conducted systematic reviews (2009–15). The two main reviews include: 1) An Agency for Healthcare Research and Quality (AHRQ) review published in 2015 (7, 26) for the National Institutes of Health Pathways to Prevention Workshop on the effectiveness and risks of long-term opioid therapy, and 2) a review conducted in 2009 (27) that examined the use of opioid for chronic non-cancer pain (CNCP) for the American Pain Society and the American Academy of Pain Medicine Clinical Practice Guideline. Both reviews identified large and persistent evidence gaps with regard to the use of chronic opioid therapy in the following areas:

- **Long-term Effectiveness of Treatment Options:** The evidence base for the long-term use of opioids for chronic pain management is surprisingly weak, given the importance of this topic. Specifically, no studies of opioid therapy versus no opioid therapy, or non-opioid alternative therapies (e.g., physical therapy, behavioral therapy, or proven complementary and alternative medicine approaches), have evaluated outcomes related to pain, function, or quality of life for longer than 1 year (7, 26). Most placebo-controlled randomized controlled trials (RCTs) were shorter than 6 weeks, and all were shorter than 16 weeks (7). Likewise, no studies examined the comparative effectiveness of opioids plus non-opioid interventions versus opioids or non-opioid interventions alone for the outcomes noted above. Finally, no studies have examined how treatment effectiveness may vary based on cause of pain, patient demographics, or comorbidities (7, 26).
- **Clinical Management—Dosing Strategies:** There is limited evidence on the effectiveness of different opioid dosing strategies to help guide clinical decision making (28).
 - **Initiating and Titrating Opioids:** Little evidence is available concerning the effects of titration with immediate-release versus sustained-release opioids on pain outcomes. Findings from three RCTs were difficult to interpret, given the differences between treatment arms in dosing protocols. No studies examined outcomes related to function, quality of life, or other abuse-related outcomes (7, 26).
 - **Dose Escalation:** The only RCT of dose escalation versus maintenance of current dose found no difference in pain, function, or risk of withdrawal due to opioid misuse (26).
 - **Alternative Dosing Strategies:** To date, no studies have examined the long-term effectiveness of short- versus long-acting opioids, short- plus long-acting opioids versus long-acting opioids alone, scheduled continuous dosing versus as-needed dosing, or opioid rotation versus maintenance of current therapy (26).
 - **Withdrawal and Opioid Tapering Protocols:** Although results from two nonrandomized studies suggest there is no difference in the effectiveness of opioid discontinuation or tapering strategies on the likelihood of opioid abstinence, these trials suffered from a number of methodological weaknesses (7). Additionally, there is insufficient evidence to demonstrate the comparative effectiveness of opioid tapering or discontinuing strategies versus continuation of opioids on such patient-centered outcomes as pain and withdraw. To date, no studies have examined the effects of discontinuing opioids on pain, function, quality of life, or withdrawal symptoms (7).

- A recent Cochrane review (2013) investigated the effectiveness of different methods designed to achieve reduction or cessation of prescribed opioid use for the management of chronic pain. The two studies included in the review were at significant risk of bias because of their small size as well as other important issues, including blinding. The review determined that no conclusions could be drawn regarding the effectiveness of interventions for opioid withdrawal in CNCP (29).
- Comparative Effectiveness of Long-Acting Opioids:
 - Limited evidence from three RCTs indicate no difference in the effectiveness of different long-acting opioids when patients are permitted to have doses titrated for adequate pain control. Additionally, all three trials suffered from a number of methodological weaknesses, and no trial was designed to examine risk for overdose, addiction, abuse, or misuse (7, 26)
 - Methadone: Although the strength of evidence is low, one study conducted in a VA setting found that methadone was associated with lower mortality risk, compared with sustained-release morphine (26).
 - A recent Cochrane review (2012) assessed the analgesic effectiveness and safety of methadone in the treatment of chronic non-cancer pain. The three studies included in the review provided little evidence of the efficacy of methadone for CNCP. No conclusions can be made regarding differences in effectiveness or side effects between methadone and placebo, other opioids, or other treatments (30).
 - Five RCTs found buccal or intranasal fentanyl more effective than placebo or oral opioids for treating acute exacerbation of chronic pain. All these studies focused on short-term treatment and immediate outcomes in the minutes or hours after administration. No study assessed the long-term benefits or harms, including accidental overdose, abuse, or addiction (26).
 - Breakthrough Pain: Only two trials evaluated the use of short-acting opioids for treatment of breakthrough pain in patients on chronic opioid therapy. The study conclusions are limited by short duration of follow-up and the lack of an active comparison arm (other opioids or non-opioid interventions) (27).
- Risk-Assessment Instruments and Risk Mitigation: There is a lack of strong evidence demonstrating the effectiveness of risk-assessment tools to predict abuse in long-term therapy. Available data are drawn from only five studies with considerable methodological flaws (26). Additionally, there have been no studies directly evaluating the efficacy of risk-mitigation strategies (patient agreements, urine drug screening, patient education, monitoring instruments, and pill counts) on adverse outcomes (e.g., abuse, addiction, and overdose) associated with long-term opioid therapy (7, 26, 28).
- Harms and Adverse Events: Although HHS has deemed prescription opioid overdose to be an epidemic in the United States, due to the alarming increase in the number of overdose-related fatalities, there is little evidence regarding the harms and adverse outcomes associated with long-term opioid therapy (20, 24, 31). For example, although observational studies have shown that long-term opioid therapy for the treatment of chronic pain is associated with increased risk for overdose, opioid use disorder, fractures, myocardial infarction, and hypogonadism with sexual dysfunction, the strength of this evidence is limited due to study confounding. Additionally, no RCTs have assessed adverse events associated with long-term opioid therapy compared with placebo or no opioid therapy for chronic pain. Furthermore, no studies have evaluated the risk for falls, infections, or

cognitive or gastrointestinal adverse outcomes associated with long-term opioid therapy compared with placebo or non-opioid therapy (26).

- **High-Risk Patients:** The majority of RCTs of opioids for CNCP excluded patients at higher risk for abuse or addiction. Studies that include these high-risk patients, who are commonly treated with opioids in clinical practice settings, are needed (27).
- **Opioid Use during Pregnancy:** No observational trials or RCTs evaluated the effects of various strategies for managing chronic pain with opioids during pregnancy (27).
- **Racial and Ethnic Minorities:** Scant evidence exists regarding the long-term use of opioids for the treatment of chronic pain among racial and ethnic minorities. Research does suggest that racial and ethnic minorities are less likely to receive opioid treatment when compared with Caucasian patients (32–35). Furthermore, there are significant barriers to this population’s access to opioid prescriptions as well as disparities in how these patients are monitored (36–37).

In addition to the research areas listed above, the Pathways to Prevention panel recommended that federal and nonfederal agencies sponsor research in the following areas (28) (verbatim):

- “Federal and nonfederal agencies should sponsor research to identify which types of pain, specific diseases, and patients are most likely to benefit and incur harm from opioids. Such studies could use a range of approaches and could include demographic, psychological, sociocultural, ecological, and biological characterizations of patients in combinations with clear and accepted definitions of chronic pain and well-characterized records for opioids and other pain medications”.
- “Federal and nonfederal agencies should sponsor the development and evaluation of multidisciplinary pain interventions, including cost-benefit analyses and identification of barriers to dissemination”.
- “Federal and nonfederal agencies should sponsor research to develop and validate research measurement tools for identification of patient risk and outcomes (including benefit and harm) related to long-term opioid use that can be adapted to clinical settings”.
- “Electronic health record vendors and health systems should incorporate decision support for pain management and facilitate export of clinical data, to be combined with data from other health systems to better identify patients who benefit from or are harmed by opioid use”.
- “Researchers on the effectiveness and harms of opioids should consider alternative designs (e.g., n-of-1 trials, qualitative studies, implementation science, secondary analysis, or phase 1 and 2 designs) in addition to RCTs”.
- “Federal and nonfederal agencies should sponsor research on risk identification and mitigation strategies, including drug monitoring, before widespread integration of these into clinical care. This research should also assess how policy initiatives affect patient/public health outcomes”.
- “Federal and nonfederal agencies and healthcare systems should sponsor research and quality improvement efforts to facilitate evidence-based decision making at every step of the clinical decision process”.
- “In the absence of definitive evidence, clinicians and healthcare systems should follow current guidelines by professional societies about which patients and which types of pain should be treated with opioids and about how best to monitor patients and mitigate risk for harm”.
- “The National Institutes of Health or other federal agencies should sponsor conferences to promote harmonization of guidelines of professional organizations in order to facilitate more consistent implementation of them in clinical care”.

5. Guidelines

A systematic review of 13 opioid-prescribing guidelines for chronic pain found (8) that:

- Two guidelines were deemed to be of high quality: one by the American Pain Society – American Academy of Pain Medicine (3) and another by the Canadian National Opioid Use Guideline Group (38).
- Seven guidelines were of intermediate quality.
- Four guidelines were not recommended for use.
- Ten guidelines were based on poor- to fair-quality information.

The guidelines for opioid prescribing generally agree on the following (8) (verbatim):

- “Benzodiazepines and opioids are a high-risk combination, particularly in elderly adults”.
- “Methadone poses risks for dose-related heart rate–corrected QT interval (QTc) prolongation and respiratory suppression due to a long half-life and unique pharmacokinetics. Guidelines generally recommend that only knowledgeable providers prescribe methadone”.
- “There is a need for caution in prescribing doses greater than 90 to 200 mg of morphine equivalents per day, in recognizing risks associated with fentanyl patches, in titrating with caution, and in reducing doses by at least 25 percent to 50 percent when switching from one opioid to another”.
- “Risk-assessment tools, written treatment agreements, and urine drug testing can be helpful when opioids are prescribed for long-term use. Recommendations from earlier guidelines are generally similar to those published recently”.
- “Given the pressing need to address opioid-related adverse outcomes, guideline developers seem to agree on forging recommendations based on relatively weak or indirect evidence now rather than waiting for more rigorous studies”.

6. Ongoing Studies

There are 13 relevant ongoing studies under the search term “long-term opioid treatment + chronic pain” and 1 relevant ongoing study under the search term “dose reduction + long-term opioid treatment” in clinicaltrials.gov. Studies with unknown status and those that focused on patients with cancer were excluded.

- The majority of the open trials are phase 2 and 3 RCT safety/efficacy trials.
- One RCT (n=276) compares benefits and harms of two prescribing strategies: 1) an opioid-intensive strategy that uses strong opioids, such as morphine, early in treatment, and 2) an opioid-avoidant strategy that optimizes non-opioid medications while delaying and minimizing opioid use. The main outcome measures include pain-related function and pain intensity. Other measures include adverse medication-related symptoms, clinically important adverse events, changes in physical and cognitive performance, and quality of life.
- One small RCT (n=30) compares nonpharmacologic options for back pain to reduce chronic opioid use. The study includes a three-arm trial of an in-elastic lumbar brace, elastic abdominal binder (standard care), and no brace (control). The main outcomes measures include pain and opioid reduction.
- One small RCT (n=50) compares cognitive behavioral therapy with a wait list (no cognitive therapy). The primary outcome measure includes number of participants with a daily opioid dose below 50 percent of initial dose and signs of hyperalgesia on quantitative sensory testing.
- One small RCT (n=95) compares a fentanyl patch in partial doses with the original patch. The primary outcome includes changes in blood concentration levels of fentanyl and nurofentanyl; the secondary outcome includes changes in the patient’s pain assessment.

7. Likelihood of Implementation in Practice

Physicians remain uncertain about best practices and worry about opioid misuse and overdose among patients, and they are eager for better evidence. However, given the lack of strong evidence supporting the long-term use of opioids, clinical decision-making is primarily guided by experience rather than evidence. A systematic review concluded that current clinical guidelines have little to no descriptions of patient input, criteria for selecting evidence, methods for formulating recommendations, and external reviews before publication (8). Likewise, only 2 of 13 chronic pain guidelines were deemed to be of high quality (8). Additional rigorous research is needed to inform physician and patient decision making and for the development of evidence-based policy guidelines. Results from comparative studies have the potential to be rapidly implemented, affect clinical decision making, and guide clinician opioid-prescribing practices, resulting in a reduction in the harms and risks associated with long-term opioid therapy for the treatment of chronic pain (7, 27).

8. Durability of Information

Given the striking lack of evidence on the comparative effectiveness of various long-acting opioids and the associated harms, well-designed studies are urgently needed (26). The new information gathered from subsequent studies could drastically improve the current evidence base.

9. Potential Research Areas/Questions

PCORI consulted with experts in the field of long-term opioid treatment to identify key research questions. A number of experts concurred that opioid therapy is beneficial for a subset of patients but may not be a valid option for all patients. To aid in clinical decision making, some experts noted that CER studies addressing the following key research questions outlined in the AHRQ report on the effectiveness and risks of long-term opioid treatment of chronic pain are needed (7):

- Effectiveness and Comparative Effectiveness:
 - In patients with chronic pain, what is the comparative effectiveness of opioids versus non-opioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?
 - In patients with chronic pain, what is the comparative effectiveness of opioids plus non-opioid interventions (pharmacological or nonpharmacological) versus opioids or non-opioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?
- Harms and Adverse Events:
 - How do the harms vary depending on (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); (2) patient demographics; (3) patient comorbidities (including past or current substance use disorder or high risk for addiction); and (4) the dose of opioids used?
- Dosing Strategies:
 - In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose thresholds on outcomes related to pain, function, and quality of life?
 - In patients on long-term opioid therapy, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?
 - In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?

- In patients on long-term opioid therapy, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?
- Additional Questions:
 - In patients with chronic pain, what is the effectiveness of risk prediction instruments in different clinical settings on patient outcomes?
 - In patients with chronic pain, what are the risks of long-term opioid therapy versus alternative treatments on endocrinological and cardiovascular harms?

One expert noted that chronic pain is a biopsychosocial issue and, given the poor evidence base demonstrating the benefits of long-term opioid use and mounting concerns about its harms, there will continue to be a national trend toward reducing opioid treatment. Suggestions for future studies included the following:

- In patients with chronic pain on long-term opioid therapy, more research on how to reduce dosage while maintaining pain control through the use of adjunctive therapies, such as biopsychosocial/cognitive interventions
- Timely studies of shared decision making for those patients already on opioids who are looking to discontinue or reduce opioid treatment
- Better understanding of the factors influencing underutilization of opioids in racial/ethnic minority populations and preferences for alternative nonpharmacologic approaches

10. Conclusions

Limited evidence suggests that opioid therapy can be effective for patients who are closely monitored; however, the challenge remains in identifying patients for whom opioid use is appropriate, the optimal drug regimens, and alternatives for those who are unlikely to benefit from opioids, while ensuring patient needs are met (28). Additional research that focuses on the following issues will be needed: (a) the effectiveness and risks of long-term opioid use for the management of chronic pain; (b) opioid dosing strategies; (c) opioid assessment and risk mitigation tools; and (d) long-term opioid treatment in high-risk patients (7, 31). In addition, based on expert guidance, more research is needed on dose reduction/withdrawal and how best to maintain pain control through the use of adjunctive therapies, given the little evidence currently available. CER on the questions above will help improve understanding of the optimal strategy for treating chronic pain while balancing potential harms.

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