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Long-term Use of Opioids for Complex Chronic Pain

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Abstract

Increased opioid prescribing for back pain and other chronic musculoskeletal pain conditions has been accompanied by dramatic increases in prescription opioid addiction and fatal overdose. Opioid-related risks appear to increase with dose. While short-term randomized trials of opioids for chronic pain have found modest analgesic benefits (a one-third reduction in pain intensity on average), the long-term safety and effectiveness of opioids for chronic musculoskeletal pain is unknown. Given the lack of large, long-term randomized trials, recent epidemiologic data suggests the need for caution when considering long-term use of opioids to manage chronic musculoskeletal pain, particularly at higher dosage levels. Principles for achieving more selective and cautious use of opioids for chronic musculoskeletal pain are proposed.

Opioids and complex chronic pain

Opioids are naturally occurring or synthetic chemicals resembling morphine in pharmacological effects, including oxycodone, morphine, hydrocodone, methadone, hydromorphone, meperidine (or pethidine), fentanyl and codeine. Opioids bind to receptors found principally in the central and peripheral nervous systems and the gastrointestinal tract. They are commonly used for:

1. Time-limited pain management of medical procedures, dental procedures, and acute injury and disease.
2. Open-ended palliative care of patients with late-stage or end-stage disease.
3. Short-term or long-term management of chronic pain conditions.

This chapter focuses on the use of opioids for care of chronic musculoskeletal pain conditions such as back pain, and addresses clinical and public health issues that arise when opioids are used long-term for these conditions. For our purposes, long-term use is defined by use of opioids for two months or more on a daily or near-daily basis. While the large majority of patients who use opioids for a few days or weeks discontinue use, the likelihood of sustained use is increased among persons who sustain daily or near daily use for more than two months.¹

Many patients using opioids long-term manifest “*complex chronic pain*”, characterized by: Absence of readily identifiable causes, a definitive differential diagnosis and/or highly

effective treatments; presence of activity limitations and disabilities, patient concerns that pain cannot be controlled, may not improve, and that underlying causes of pain make it unsafe to resume normal activities; Presence of diffuse pain and/or clinically significant depression and anxiety. While the pain status of chronic pain patients using opioids long-term is highly variable, many chronic pain patients using opioids long-term have some or many of these features of complex chronic pain.²

Care of patients using opioids long-term is also complex. Chronic pain conditions for which opioids are most often prescribed include back and neck pain, osteoarthritis and extremity pains, shoulder pain, headache, orofacial pain, pelvic pain, and fibromyalgia or chronic widespread pain.³ These common conditions are typically managed in primary care settings where it is difficult to monitor chronic opioid therapy (COT) as closely as envisioned by expert guidelines. Expert guidelines recommend comprehensive evaluation of patients being considered for COT, development of a care plan and treatment agreements to guide opioid management, close monitoring with frequent check-back visits, and periodic use of urine drug screening.⁴ Unfortunately, COT management in primary care settings usually does not conform to these recommendations. Krebs et al. found that of 7 guideline-recommended monitoring practices, the mean number documented in a 6-month period was 1.7, with pain reassessment the most common.⁵ Only 11% of COT patients had a documented treatment agreement in their medical record. Starrels et al. found that only 8% of COT patients had urine drug screening and only half had regular monitoring visits.⁶ Although these recommended practices are prudent, no well-controlled research has determined whether enhanced COT monitoring reduces risks of opioid abuse, overdose or other potential adverse outcomes.⁷

While clinicians emphasize the importance of the patient-provider relationship in chronic pain care, they report difficulties in caring for chronic pain patients when they feel pressured to prescribe opioids.⁸ A review concluded that treatment of chronic pain “may be further complicated when patients and health care providers have differing goals and attitudes concerning treatment. Difficulties in collaborative treatment decision making may result.”⁹ One study found that over half of the primary care physicians surveyed agreed that their attitudes were influenced by experiences with chronic pain patients abusing prescription pain medicines.¹⁰ Not only are chronic pain conditions managed with opioids often complex, the clinical context in which opioids are managed is also challenging.

Trends in opioid prescribing

Global consumption of strong opioids (in morphine equivalent units) increased more than 30-fold from 1980 to 2010.¹¹ However, there are substantial differences in opioid consumption between countries. In 2010, countries with the highest per capita consumption of strong opioids included the United States, Canada, Switzerland, Germany, Austria, Denmark, Australia, the United Kingdom, New Zealand, and other countries with highly developed market economies. Countries in Africa and Asia with developing market economies tend to have the lowest per capita consumption of opioids. Barriers to opioid access for humane management of procedural pain, severe acute pain, and palliative care of

late-stage and end-stage disease remain a significant problem in many parts of the developing world.¹²

The predominance of opioids prescribed in developed market economies are for management of chronic musculoskeletal pain conditions, like back pain and osteoarthritis. There is inadequate evidence regarding the appropriate role of opioids in long-term pain management of these conditions.⁷ This contributes to variation in COT prescribing between different countries, and between regions and individual prescribers within the same country. For example, in the United States there were 693 milligrams (morphine equivalents) of strong opioids prescribed per capita in 2010, compared to 335 milligrams per capita in the United Kingdom, 205 milligrams per capita in the Netherlands, and 144 milligrams per capita in Italy.¹¹ Within the U.S., there is large regional variation in opioid consumption. For example, in 2002 there was a 23-fold difference between the states with the highest and lowest opioid consumption in the U.S. Medicaid insurance program.¹³ Such differences invite a question: *Does more liberal opioid prescribing for long-term chronic pain management yield more or less favorable outcomes?*

In the absence of data from large-scale, long-term clinical trials evaluating benefits and harms of COT, it has proven difficult to reconcile harms associated with increased opioid prescribing in the United States with health benefits claimed by some patients and clinicians. While short-term trials suggest that the average benefit of time-limited opioid use for chronic pain amounts to a one-third reduction in pain intensity, with less robust benefits for functional outcomes, the long-term safety of COT has not been established.^{4, 7, 14–16} Randomized trials evaluating opioid for chronic pain have contributed only about 1500 person-years of observation,¹⁷ too little data to provide reliable estimates of health risks. In contrast, there have been 1.8 million person-years in trials of antihypertensive agents, 753,000 person-years in trials evaluating statins, and 117,000 person-years in trials evaluating non-steroidal inflammatory drugs (NSIADs).^{18–20}

An epidemic of prescription opioid abuse and overdose

As opioid prescribing for chronic pain has increased, levels of prescription opioid addiction and overdose have become epidemic. Addiction to prescription opioids is defined by: using more opioids than intended; hazardous use; persistent desire or unsuccessful efforts to cut down; social or interpersonal problems related to opioid use; opioid craving; psychological and/or physical problems related to opioid use.²¹ Tolerance and physiological dependence are not considered in diagnosing prescription opioid use disorder. However, physiological dependence can make it more difficult to discontinue opioid use from higher dose regimens if problems should arise.²² From 1999 to 2009, the rate of drug abuse treatment admissions for non-heroin opioids in the U.S. grew almost sixfold, to 140,000 a year, resulting in over three-quarters of a million addiction treatment episodes in that time span.²³

Fatal overdoses involving opioid analgesics in the U.S. increased four-fold from 1999 to 2010, to over 16,000 a year.^{24, 25} Hospitalizations for prescription opioid poisoning in the U.S. doubled from 1999 to 2006.²⁶ Ecological studies of area variation in opioid use in the United States and Canada have found that areas with higher exposure to medically

prescribed opioids also have greater opioid-related morbidity and mortality.^{27–34} Since 1990, life expectancy among Caucasian Americans with low education has dropped by four years,³⁵ an decline partially attributable to increased rates of fatal prescription drug overdose among young people.³⁶ In 2011, the White House Office of National Drug Control Policy declared an epidemic of prescription drug misuse and overdose, stating: “*Prescription drug misuse and abuse is a major public health and public safety crisis. As a nation, we must take urgent action to ensure the appropriate balance between the benefits of these medications and the risks they pose.*”³⁷ There is an emerging consensus in the U.S. and Canada that steps need to be taken to reduce unintended harms resulting from increased opioid prescribing.

Why opioid dose matters

Risks associated with COT increase with opioid dose.^{38–42} Risks to the broader community rise with increased dose as well. Prescription opioids used non-medically are most often obtained from family or friends or from home medicine cabinets.⁴³ For this reason, the amount of opioid medication available for diversion in the community is affected by the prevalence of high dose COT, since over 60% of all legally prescribed morphine equivalents are dispensed to COT patients on higher-dose regimens.⁷ Thus, prescribed dose influences the volume of opioids available for diversion and for non-medical use.

Opioid risks that increase with dose include risks of overdose^{38, 40, 41}, serious fractures,^{39, 42} depression,⁴⁴ and other adverse health effects.¹⁶ Clinical guidelines have always urged care in prescribing opioids, but there has not been agreement of guidance regarding COT dose.^{45, 46} Some experts recommend a low-to-moderate dose ceiling, while others advocate increasing a patient’s opioid dose until pain is controlled, with no dose ceiling.^{47,46} However, we do not know if these two distinctly different COT dosing strategies result in long-term differences in pain outcomes for patients, and we lack evidence from long-term controlled trials regarding differences in COT effectiveness and safety by dose.^{7, 14, 15, 48}

The risk stratification paradigm

With growing recognition of potential opioid-related harms, there has been increased emphasis on clinical evaluation of prescription opioid abuse risk factors to inform patient selection and monitoring.^{4, 49} An assumption underlying risk stratification is that accurate prediction of opioid abuse risks is possible. It has been claimed that abuse risks are low among patients who do not have a personal or family history of substance abuse, and without significant psychological disorders.^{50, 51} However, recent research calls these conclusions into question. Among COT patients, aberrant opioid use behaviors are common, including: purposeful oversedation (24%); use of alcohol to relieve pain (20%); use of higher opioid doses than prescribed (37%); and concomitant use of opioids and heavy drinking (12%).^{52–54} Recent studies have found prescription opioid addiction among 4% to 26% of COT patients.^{53, 55, 56} These results suggest that prescription drug abuse risks among COT patients are comparable to addiction risks among persons with enduring exposure to other potentially addictive substances, such as alcohol, tobacco and illicit drugs.⁵⁷

Patient risk factors

Initial studies reported good to excellent prediction of aberrant opioid use behaviors using various screeners.^{58–62} These screeners assessed patient risk factors for opioid misuse including substance use disorder history, family history of substance use disorder, and significant psychological problems. However, Chou et al.'s⁶³ structured review of opioid misuse prediction concluded that, “only limited evidence exists to determine optimal methods for prediction and identification of aberrant drug-related behaviors”, a conclusion also supported by Turk et al.'s review.⁶⁴ Citing methodological shortcomings of existing studies, Chou's review⁶³ noted, “...because the methods used to define aberrant drug-related behaviors did not distinguish relatively less serious from more serious behaviors...the clinical importance of their identification is unclear”. Only one study has predicted risks of prescription opioid abuse among COT patients based on patient variables and duration of opioid use. Hojsted et al.⁶⁵ found 82% sensitivity but only 58% specificity in predicting prescription opioid addiction.

Drug regimen risk factors

Since opioid dose increases physiological dependence, making discontinuation more difficult, dose escalation may influence risks of opioid misuse and abuse. Cross sectional studies have found that COT patients receiving high opioid dose more often have substance abuse indicators and are more likely to report concerns about their ability to control opioid use.^{44, 54, 66–69} Over 80% of COT patients on higher doses sustained higher dose opioid use one year later, with sustained opioid use observed among patients with opioid-related problems.²²

Expert guidelines assert that around the clock dosing, with long-acting opioids, reduces risks of addiction by providing more stable opioid blood levels, improved pain control, and reduced reinforcement of problematic drug use behaviors.^{70, 71} However, evidence on whether time-scheduled dosing improves pain control and reduces addiction risks is limited. COT patients using time-scheduled dosing, compared to those using pain-contingent dosing, received substantially higher average daily doses and were much more likely to report concerns about ability to control use of opioid analgesics, while pain control and satisfaction with opioid analgesics did not differ.⁷²

Data questioning COT Effectiveness

Observational studies have found that patients using opioids, and those on higher dose regimens, have poorer functional status and lower quality of life than patients not using opioids or patients on low-dose regimens.^{73–77} Cohort studies of worker's compensation patients found that those using opioids are delayed in returning to work relative to patients not using opioids and patients receiving higher opioid dose are also delayed returning to work relative to patients on lower opioid doses.^{78–82} Primary care back pain patients using opioids initially have also been found to have greater self-reported disability at follow-up after adjusting for case-mix.⁸³ Patients receiving rehabilitative services withdrawn from opioids have shown improved pain and function.^{84–91} These results could be explained by indication bias or by adverse selection, if patients with more severe pain dysfunction or a

less favorable prognosis are more likely to use opioids and to escalate to higher opioid doses. In fact, evidence suggests that patients with affective illness and other unfavorable prognostic indicators are more likely to receive COT, more likely to use opioids long-term, and more likely to escalate dose.^{66, 67, 69, 92–96} Nonetheless, these studies question the assumption, based on short-term trials, that long-term opioid use is effective.

Research gaps

A recent U.S. Food and Drug Administration (FDA)-sponsored conference concluded that lack of data on safety of opioids for long-term management of chronic pain constitutes a major gap in knowledge.⁹⁷ There is a spectrum of potential adverse outcomes that clinical studies or epidemiological research has found to be associated with opioid use,¹⁶ but these adverse outcomes related to opioids have received only limited research attention:

Respiratory depression – Opioid overdose, breathing problems during sleep;

Falls and fractures - Hip or pelvis fractures;

Gastrointestinal effects - Chronic constipation, intestinal blockage;

Hormonal effects - Hypogonadism, impotence, infertility, osteoporosis;

Cognitive and neurophysiologic effects - Sedation, disruption of sleep, hyperalgesia,;

Psychosocial effects - Depression, anxiety, deactivation, apathy;

Addiction - Drug addiction or misuse.

Other effects - Dry mouth that may lead to tooth decay.

In assessing COT risks, there is a need for controlled research that assesses the full spectrum of health risks of opioids, relative to benefits. There is also a need for research that evaluates the comparative safety of opioids relative to other analgesics are commonly used for management of chronic musculoskeletal pain, such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Accumulating evidence regarding NSAID risks resulted in the American Geriatrics Society to preferentially recommend opioids over NSAIDs for management of chronic pain,⁷¹ but this recommendation was not based on a direct comparison of the comparative safety of opioids relatively to NSAIDs.

Practice points

Given uncertainty about the long-term effectiveness of COT, and growing evidence that potential risks and harms are greater than initially believed, use of opioids for long-term management of chronic pain should be considered with caution commensurate with the potential risks. While we await better evidence regarding COT effectiveness, practical strategies for protecting patient safety should be implemented on a trial basis and effects on patient outcomes evaluated by clinicians and by researchers. Possible approaches to reducing opioid-related risks were recently proposed in a collaborative meeting of primary care physicians and pain specialists with relevant expertise convened in Seattle in 2012. Practice points achieve more selective and cautious opioid prescribing than current practice

in countries where COT is frequently prescribed, like the United States, are summarized in Table 1.

Summary

Increased opioid prescribing for common chronic pain conditions has been accompanied by dramatic increases in prescription opioid addiction and fatal overdose. Opioid-related risks appear to increase with dose. While short-term randomized trials of opioids for chronic pain have found modest analgesic benefits (a one-third reduction in pain intensity on average), the long-term safety and effectiveness of COT for chronic musculoskeletal pain is unknown. Given the lack of adequate trials data, recent epidemiologic studies suggest the need for caution when considering long-term use of opioids to manage chronic musculoskeletal pain, particularly at higher dosage levels.

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Table 1

Practice points for selective and cautious opioid prescribing among patients with chronic musculoskeletal pain conditions*

Principles for All Chronic Non-Cancer Pain Patients

- 1 **Self-care is the foundation for effective chronic non-cancer pain care** - Patient efforts to remain active and sustain rewarding life activities usually matter more than treatments prescribed for chronic pain.
- 2 **Your relationship with the patient supports effective self-care** - Listening, empathy, and encouraging patients to remain active and sustain rewarding life activities characterizes excellent care for patients with chronic pain.
- 3 **Guide care by progress toward resuming activities** - To track outcomes, have patients rate their ability to participate in rewarding life activities that pain makes difficult on a 0–10 scale (where 0 is “no difficulty” and 10 is “extreme difficulty”). Monitor return to work. For sedentary patients, consider tracking gradual increases in walking. Guiding care by changes in pain intensity should not be the primary indicator of successful care.
- 4 **Prioritize long-term effectiveness over short-term pain relief** - Differentiate treatments offered for short-term pain relief from steps patients take to resume activities. Short-term pain relief can be helpful, but long-term benefits of medications for chronic non-cancer pain are often modest, and risks may outweigh potential benefits.

Principles When Considering Long-term Use of Opioids

- 1 **Put patient safety first** - Find common ground with patients by emphasizing their safety. Risks of long-term opioid use are significant, while benefits are typically modest. Possible adverse effects include addiction, overdose, dependence, depression, cognitive impairment, chronic constipation, motor vehicle accidents, and serious fractures due to falls, among others.
- 2 **Think twice before prescribing long-term opioids for axial low back pain, headache and fibromyalgia** - The long-term benefits of opioids for these conditions are unproven, while risks of addiction, overdose and other serious adverse effects are significant.
- 3 **Systematically evaluate risks** - Do not consider a therapeutic trial of opioids for chronic non-cancer pain before assessing risks of opioid misuse and abuse by taking a thorough history, reviewing the medical record, and checking Prescription Drug Monitoring Program data. Ask about past or current alcohol, tobacco and drug abuse, and mental health problems. Do not overestimate your ability to identify high risk patients. Risks of long-term opioid use are substantial, so be cautious when considering COT, especially for higher risk patients.
- 4 **Consider intermittent opioid use** - Continuous use of long acting opioids has not been proven more effective or safer than intermittent use of short-acting opioids. Time-scheduled opioid prescribing has not been proven to reduce risks of opioid misuse or addiction. Higher doses with around-the-clock use may increase risks. Consider PRN prescriptions of short acting opioids to minimize risks of tolerance, dependence and dose-related medical risks of opioids. When opioids are prescribed for short-term pain management, set clear expectations for duration of use. Prescribe no more than needed for acute pain management—often a few days to a one week supply.
- 5 **Do not sustain opioid use long-term without decisive benefits** - Initial evaluation of long-term opioid use should be based on a therapeutic trial lasting no more than 90 days, preferably less. Long term use of opioids should only be continued if decisive benefits are observed during the trial. Opioids should not be continued if improved function is not sustained. Involve the patient in determining functional goals for therapy. Continually monitor the benefit-to-harm ratio as benefits may decrease while harms accrue over time.
- 6 **Keep opioid doses as low as possible** - Reaching doses of 50 to 100 milligrams morphine equivalents or higher should trigger re-evaluation of the therapy. Risks increase with dose, but benefits of higher doses have not been established. Discontinuation is substantially more difficult at high dose.

Principles for more selective and cautious opioid prescribing*
Principles for Patients Using Opioids Long-term

- 1 **Clearly communicate standardized expectations to reduce risks** - Opioids have important hazards for patients, for family members, and for the community. Set clear expectations for use to reduce patient risks and for protecting others from unintentional or intentional diversion. Expectations should be standardized across all clinicians in your practice setting and communicated to patients verbally and with simple written materials.
- 2 **Adhere to recommended precautions** - Close and sustained monitoring of COT is the standard for care. This includes asking about potential opioid misuse and about adverse behavioral, psychological and medical effects of opioids. Check urine drug screening results and Prescription Drug Monitoring data periodically. These precautions should increase in frequency and stringency for patients on regimens of 50 to 100 milligrams morphine equivalent dose or greater, and for patients with risk factors for opioid misuse. These safety precautions do not guarantee patient safety, so vigilance and caution are essential.
- 3 **Avoid prescribing opioids and sedatives concurrently** - Concurrent use of opioids and other CNS depressants increases risks of overdose and other adverse effects. Prescribing opioids and sedatives concurrently is not recommended.

- 4 **Revisit discontinuing opioids or lowering dose** - Regularly reassess whether doses can be reduced or opioids discontinued entirely. Many patients using opioids long-term are ambivalent about opioid use. Patients may be open to a trial of a slow taper. Opioids should be tapered when problems arise or if decisive benefits for function are not sustained. If a patient is diverting or engaging in high risk opioid misuse, discontinuation is mandatory. Non-fatal overdose should prompt immediate reduction of opioid dose or tapering off completely.
- 5 **Identify and treat prescription opioid misuse disorders** – When identified, patients with prescription opioid abuse or addiction should be treated rather than discharged from care. Know locally available referral options for addiction treatment including buprenorphine/naloxone treatment, methadone maintenance and counseling. Abrupt detoxification is not the standard of care, and is not supported by evidence, as the primary option for prescription opioid addiction.

* These principles are not intended for palliative care of chronic pain at end of life.

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