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# Long-Term Opioid Therapy Reconsidered

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In the past 20 years, primary care physicians have greatly increased prescribing of long-term opioid therapy. However, the rise in opioid prescribing has outpaced the evidence regarding this practice. Increased opioid availability has been accompanied by an epidemic of opioid abuse and overdose. The rate of opioid addiction among patients receiving long-term opioid therapy remains unclear, but research suggests that opioid misuse is not rare. Recent studies report increased risks for serious adverse events, including fractures, cardiovascular events, and bowel obstruction, although further research on medical risks is needed. New data indicate that opioid-related risks may increase with dose. From a societal perspective, higher-dose regimens account for the majority of opioids dispensed, so cautious dosing may reduce both diversion potential and patient risks for adverse effects. Limiting long-term opioid therapy to patients for whom it provides decisive benefits could also reduce risks. Given the warning signs and knowledge gaps, greater caution and selectivity are needed in prescribing long-term opioid therapy. Until stronger evidence becomes available, clinicians should err on the side of caution when considering this treatment.

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For two decades, opioid therapy for chronic noncancer pain has been contentious and controversial, but two points are now widely agreed on. First, chronic pain has substantial negative effects. About 25% of adults have moderate to severe chronic pain, and about 10% have disabling chronic pain that limits work and family activities (1). Patients who seek medical care for chronic pain need and deserve compassionate care and evidence-based pain management. Second, the increase in prescribing opioids to manage chronic noncancer pain has been accompanied by alarming increases in diversion of prescription opioids, opioid misuse and abuse, and fatal overdoses involving prescription opioids (2). This situation is urgent, resulting in a recent call for action by the federal government (2).

Debate about long-term opioid therapy seems to pit commitment to compassionate care of patients with chronic pain against adequate response to an epidemic of prescription opioid abuse and overdose. These goals need not be mutually exclusive. Clinicians and their professional societies can take action now to increase the margin of safety for patients and society while preserving access to long-term opioid therapy for carefully selected and closely monitored patients. We propose steps to achieve these objectives.

## Effectiveness of Long-Term Opioid Therapy

Perceptions that long-term opioid therapy typically yields long-lasting benefits for patients with chronic noncancer pain are not supported by strong evidence. Controlled trials lasting 1 to 6 months suggest modest pain relief relative to placebo, but no long-term studies have determined whether analgesic efficacy is maintained (3–5). Studies of long-term opioid therapy versus alternative treatments are few and suggest limited advantages for opioids (4, 5). The 2009 evaluation of evidence for long-term opioid therapy by the American Pain Society and the American Academy of Pain Medicine rated 21 of their 25 recommendations as based on "low-quality evidence" (3). A recent survey of primary care patients receiving long-term opioid therapy found that most continued to report moderate to severe pain and that functional outcomes were often poor (6). Nonetheless, clinicians report that some patients with chronic pain treated with opioids seem to experience meaningful benefits, reflecting patient variability in response to long-term opioid therapy.

## Risks of Long-Term Opioid Therapy

The original case for using long-term opioid therapy to treat chronic noncancer pain was based on safety assumptions that subsequent experience calls into question. In 1996, the American Pain Society and the American Academy of Pain Medicine issued a consensus statement supporting long-term opioid therapy (7). This statement acknowledged the dangers of imprudent opioid prescribing but concluded that the risk for de novo addiction was low; respiratory depression induced by opioids was short-lived, occurred mainly in opioid-naive patients, and was antagonized by pain; tolerance was not a common problem; and efforts to control diversion should not constrain opioid prescribing. Unfortunately, experience regarding the risks for opioid addiction, misuse, and overdose in community practice has failed to confirm these assertions (2, 4, 8–17).

Consistent estimates of the prevalence of prescription opioid abuse among primary care patients receiving long-term opioid therapy remain elusive. The few surveys in community practice estimate rates of prescription opioid abuse from 4% to 26% (4, 8–10), but recent studies suggest that potentially serious opioid misuse is not rare (8, 10, 11). For example, Fleming and colleagues conducted 2-hour interviews with 801 patients receiving long-term

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opioid therapy who were being treated by 235 Wisconsin physicians (8). They found rates of 26% for purposeful oversedation, 39% for increasing dose without prescription, 8% for obtaining extra opioids from other doctors, 18% for use for purposes other than pain, 20% for drinking alcohol to relieve pain, and 12% for hoarding pain medications.

Widespread opioid prescribing for chronic pain leads to greater opioid availability in homes and communities, with public health consequences. According to the Centers for Disease Control and Prevention, fatal overdoses involving opioid analgesics have increased sharply over the past decade (12). Currently, more than 13 000 deaths from overdose per year involve prescription opioids, and deaths from drug overdose have surpassed motor vehicle accidents as the leading cause of injury death for persons 35 to 54 years of age (13). The risk for opioid overdose increases markedly with dose among patients receiving long-term opioid therapy (14–16). Use of diverted prescription opioids by adolescents is now among the most common forms of drug abuse (17). Because diversion can result in addiction or fatal overdose, decisions about prescribing need to take the risks to family and community into account in addition to the direct risks to patients.

Direct risks of long-term opioid therapy are not limited to opioid addiction and overdose. Potential medical risks include serious fractures, breathing problems during sleep, hyperalgesia, immunosuppression, chronic constipation, bowel obstruction, myocardial infarction, and tooth decay secondary to xerostomia. Clinical data suggest that neuroendocrine dysfunction may be common in both men and women, potentially causing hypogonadism, erectile dysfunction, infertility, decreased libido, osteoporosis, and depression (18). Recent studies linked higher opioid dose to increased opioid-related mortality (15, 16). Controlled observational studies reported that long-term opioid therapy may be associated with increased risk for cardiovascular events (19, 20). A descriptive study of 133 persons aged 65 years or older receiving long-term opioid therapy found that 5% were hospitalized for opioid-related adverse events (21). Nonetheless, recent guidelines from the American Geriatrics Society concluded that all patients with moderate to severe pain be considered for opioid therapy (22). This recommendation was based in part on the unfavorable safety profile of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for managing chronic pain in older adults. However, a subsequent meta-analysis concluded that the safety of long-term opioid therapy in elderly patients is not yet established (5). We conclude that medical risks of long-term opioid therapy have not been adequately studied, although recent research identifies important risks associated with opioid dose. Additional evidence is needed to determine the net benefit of long-term opioid therapy by dose, weighing its benefits against the full spectrum of possible adverse effects.

## Safer Prescribing

Guidelines on long-term opioid therapy advocate medication management by a single physician, clinical risk evaluation, treatment agreements, periodic monitoring, urine drug screening, and documentation of treatment in the medical record (23). Various screening tools have been recommended to identify high-risk patients (24, 25), but the evidence supporting screening as a means of risk reduction is limited. Moreover, primary care physicians do not consistently adhere to recommended prescribing practices (26). Guideline-based prescribing practices, while prudent, may alone be insufficient to ensure desired levels of opioid safety in community practice.

Safer opioid prescribing for chronic pain now depends largely on physician decisions. Practical steps to

*Table.* **Cautious Prescribing Practices When Considering Therapy With Opioids***

| | Acute Pain Management | Chronic Pain Management |
|---|---|---|
| **Do** | Explain that opioids are for time-limited use.<br>Limit the prescription to the expected duration of acute pain management. | Talk with patients about therapeutic goals, risks of opioids, realistic benefits, and prescribing ground rules.<br>Screen patients for depression and other psychiatric disorders and for substance abuse history before initiating long-term opioid therapy.<br>Realize that patients are reluctant to disclose a history of substance abuse.<br>Explain to patients that discontinuing opioid therapy may be difficult. |
| **Don't** | Stock your patients' medicine cabinets with unused opioids. Limit all initial and refill prescriptions for acute pain.<br>Start long-term use of opioids by accident. Long-term opioid prescribing should only occur after careful patient evaluation and discussion.<br>Prescribe extended-release opioids for acute pain or to opioid-naive patients. | Initiate long-term opioid therapy before considering safer alternatives.<br>Continue long-term opioid therapy in patients who show no progress toward treatment goals, defined by increased function and reduced pain.<br>Assume that patients know how to use opioids safely.<br>Assume that patients use opioids as you intend.<br>Start treating patients with long-term opioid therapy if you are not prepared to stop if benefits are not achieved or problems arise.<br>Assume that patients are doing well with long-term opioid therapy without careful evaluation.<br>Abandon patients with a prescription drug problem. |

* Adapted from reference 27.

reduce opioid-related harms include more careful patient selection before initiating long-term opioid therapy, increased caution in dose escalation, and closer monitoring. Following guideline recommendations (23), clinicians should taper and discontinue long-term opioid therapy in patients who do not benefit from it or who seriously misuse opioids.

Increased selectivity before and after initiation of long-term opioid therapy and greater caution in dose escalation could increase safety by reducing the direct risks for opioid-related adverse events. It would also limit the amount of opioid medication in the community, decreasing the potential for diversion. At Group Health Cooperative in 2008, 87% of all opioid morphine equivalents prescribed for acute or chronic pain were dispensed to patients receiving long-term opioid therapy. Sixty percent of all opioid morphine equivalents prescribed were dispensed to patients receiving a long-term morphine equivalent dose of 50 mg or greater. These patients comprise only about 20% of all patients receiving long-term opioid therapy. More judicious opioid prescribing for chronic pain, particularly increased caution with higher doses, could substantially reduce the opioids available for diversion.

## Balancing the Benefits and Risks of Long-Term Opioid Therapy

In response to epidemic levels of prescription opioid abuse, misuse, and overdose, concerned physicians and researchers formed a group to identify practical approaches to more cautious opioid prescribing in community practice. Physicians for Responsible Opioid Prescribing is a nonprofit organization with no pharmaceutical industry funding or ties. This group developed educational materials for clinicians, advised by experts on long-term opioid therapy from general medicine, pain medicine, and addiction medicine. The **Table** summarizes guidance on opioid prescribing for acute and chronic pain (27). Physicians for Responsible Opioid Prescribing advocates acute pain management strategies that reduce the chance of unplanned transitions to long-term use of opioids. For chronic pain management, they advocate strategies acknowledging that long-term opioid therapy entails medical, psychosocial, and addiction risks that need to be disclosed and managed. Although it is not known whether such guidance will mitigate risks, it reflects steps that clinicians can take to err on the side of caution.

Significant gaps in knowledge regarding the effectiveness and safety of long-term opioid therapy remain (3–5). Given compelling evidence of increased societal harms, the relevant professional societies should reconsider practice guidelines. Guidelines for long-term opioid therapy should not be developed by the field of pain medicine alone. Rather, experts from general medicine, addiction medicine, and pain medicine should jointly reconsider how to increase the margin of safety.

Until we better understand how to ensure the safety of long-term opioid therapy, gaps in knowledge and uncertain risks must be carefully considered. At present, physicians need to be selective, cautious, and vigilant when considering long-term opioid therapy.

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