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POSITION PAPER

National Institutes of Health Pathways to Prevention Workshop: The Role of Opioids in the Treatment of Chronic Pain

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This National Institutes of Health (NIH) Pathways to Prevention Workshop was cosponsored by the NIH Office of Disease Prevention (ODP), the NIH Pain Consortium, the National Institute on Drug Abuse, and the National Institute of Neurological Disorders and Stroke. A multidisciplinary working group developed the workshop agenda, and an evidence-based practice center prepared an evidence report through a contract with the Agency for Healthcare Research and Quality to facilitate the workshop discussion. During the 1.5-day workshop, invited experts discussed the body of evidence, and attendees had opportunities to provide comments during open discussion periods. After weighing evidence from the evidence report, expert presentations, and public comments, an unbiased, independent panel prepared a draft report that identified research gaps and future research priorities. The report was posted on the ODP Web site for 2 weeks for public comment. This article is an abridged version of the panel's full report, which is available at https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/opioids-chronic-pain/workshop-resources#finalreport.

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For author affiliations, see end of text.
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Chronic pain affects an estimated 100 million Americans, or one third of the U.S. population. Approximately 25 million have moderate to severe chronic pain that limits activities and diminishes quality of life. Pain is the primary reason that Americans receive disability insurance, and societal costs are estimated at between $560 billion and $630 billion per year due to missed workdays and medical expenses.

Although there are many treatments for chronic pain, an estimated 5 to 8 million Americans use opioids for long-term management. Opioid prescriptions and use have increased dramatically over the past 20 years; the number of opioid prescriptions for pain treatment was 76 million in 1991 but reached 219 million in 2011. This striking increase has paralleled increases in opioid overdoses and treatment for addiction to prescription painkillers. Yet, evidence also indicates that 40% to 70% of persons with chronic pain do not receive proper medical treatment, with concerns for both overtreatment and undertreatment. Together, the prevalence of chronic pain and the increasing use of opioids have created a "silent epidemic" of distress, disability, and danger to a large percentage of Americans. The overriding question is: Are we, as a nation, approaching management of chronic pain in the best possible manner that maximizes effectiveness and minimizes harm?

On 29 and 30 September 2014, the National Institutes of Health (NIH) convened a Pathways to Prevention workshop, "The Role of Opioids in the Treatment of Chronic Pain." The workshop involved a panel of 7 experts, featured more than 20 speakers, and was informed by a systematic review conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (1). The EPC review addressed evidence about the long-term effectiveness of opioids, the safety and harms of opioids, the effects of different opioid management strategies, and the effectiveness of risk mitigation strategies for opioid treatment.

Context

The expert panel considered in detail many contextual issues that affect understanding about the dilemma of opioid use and chronic pain (see the full report at https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/opioids-chronic-pain/workshop-resources#finalreport). Some of these are discussed in the following paragraphs.

The burden of dealing with unremitting pain can be devastating to a patient's psychological well-being and can negatively affect their ability to maintain gainful employment or achieve meaningful professional advancement. It can affect relationships with spouses and significant others; may limit engagement with friends and other social activities; and may induce fear, demoralization, anxiety, and depression.

Health care providers, who are often poorly trained in the management of chronic pain, are sometimes quick to label patients as "drug-seeking" or as "addicts" who overestimate their pain. Some physicians "fire" patients for increasing their dose or for merely voicing concerns about their pain management. These experiences may make patients feel stigmatized or feel as if others view them as criminals and may heighten fears that their pain-relieving medications will be taken away, leaving them in chronic, disabling pain.

Some patients who adhere to their prescriptions may believe that their pain is managed adequately, but others using opioids in the long term may continue to have moderate to severe pain and diminished quality of life. Although many physicians believe that opioid treatment can be valuable for patients, many also believe that patient expectations for pain relief may be

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unrealistic and that long-term opioid prescribing can complicate and impair their therapeutic alliance with the patient.

Although some patients gain substantial pain relief from opioids and do not have adverse effects, these benefits must be weighed against the problems caused by the vast number of opioids now prescribed and the fact that opioids are finding their way illicitly into the public arena. The Substance Abuse and Mental Health Services Administration's 2013 National Survey on Drug Use and Health found that, among persons aged 12 years or older who were abusing analgesics, 53% reported receiving them for free from a friend or relative (2). According to the Centers for Disease Control and Prevention, approximately 17 000 overdose deaths involving opioids occurred in 2011 (3). From 2000 to 2010, the number of hospitalizations for addiction to prescription opioids increased more than 4-fold to more than 160 000 per year. In 2010, one out of every eight deaths among persons aged 25 to 34 years was opioid-related (4). In a 3-year period (2003 to 2006), more than 9000 children were exposed to opioids.

Many historical factors have influenced opioid use. All currently available extended-release opioids have been approved for treatment of chronic pain on the basis of 12-week efficacy studies, although there are safety data for extended-release opioids from studies lasting a year (mostly open-label studies). Many immediate-release opioids came on the market without approval from the U.S. Food and Drug Administration (FDA) for treatment of acute pain, but all received approval in recent years. New opioids that were introduced on the market over the past decade, particularly those with extended-release formulations, were attractive to patients and clinicians, who perceived them as safe and effective despite limited evidence. Physicians have little training in how to manage patients with chronic pain and appropriately prescribe medications for them. Physicians are often unable to distinguish among persons who would use opioids for pain management and not develop problems with misuse, those who would use them for pain management and then become addicted, and those who request a prescription because of a primary substance use disorder.

Given these complexities, the panel struggled to strike a balance between the ethical principles of beneficence and doing no harm—specifically, between the clinically indicated prescribing of opioids on one hand and the desire to prevent inappropriate prescription abuse and harmful outcomes on the other. These goals should not be mutually exclusive, and in fact, approaches that attempt to achieve both simultaneously are essential to advance the field of chronic pain management. The panel also grappled with making recommendations in the face of little empirical evidence and eventually formulated advice based on its synthesis of the EPC report (1), workshop presentations that focused on clinical experience, and smaller trials and cohort studies.

CLINICAL ISSUES

Patient Assessment and Triage

Chronic pain is a complex clinical issue requiring an individualized, multifaceted approach. It spans a multitude of conditions, with varied causes and presentations. Persons living with chronic pain are often lumped into a single category, and treatment approaches are sometimes generalized without supporting evidence. In addition, although pain is a dynamic phenomenon that waxes and wanes over time, it is often viewed and managed with a static approach. For many reasons, including lack of knowledge, practice settings, resource availability, and reimbursement structure, clinicians are often ill-prepared to diagnose, appropriately assess, treat, and monitor patients with chronic pain.

The panel identified several important management issues for clinicians. First, they must recognize that patients' manifestation of and response to pain will vary, with genetic, cultural, and psychosocial factors all contributing to this variation. Clinicians' response to patients with pain may differ because of preconceived notions and biases based on racial, ethnic, and other sociodemographic stereotypes. Treating pain and reducing suffering do not always equate, and patients and clinicians sometimes have disparate ideas about successful outcomes. A more holistic approach to the management of chronic pain that is inclusive of the patients' perspectives and desired outcomes should be the goal.

Patients, providers, and advocates all agree that opioids are an effective treatment for chronic pain for a subset of patients and that limiting, disrupting, or denying access to opioids for these patients can be harmful. These patients can be safely monitored by using a structured approach that includes optimization of opioid therapy, management of adverse effects, and follow-up visits at regular intervals.

The fact that some patients benefit while others do not, or may in fact be harmed, highlights the challenge of appropriate patient selection. Data are lacking on the accuracy and effectiveness of risk prediction instruments for identifying patients at highest risk for adverse outcomes (such as overdose or development of an opioid use disorder). Yet, the panel heard from a workshop speaker that longitudinal studies have demonstrated risk factors (for example, substance use disorders and comorbid psychiatric illnesses) that are associated with these harmful outcomes, and some studies show that patients who are at high risk are most likely to be prescribed opioids and higher doses of them.

Although evidence supporting specific risk assessment tools is insufficient, our consensus was that management of chronic pain should be individualized and should be based on a comprehensive clinical assessment that is conducted with dignity and respect and without value judgments or stigmatization of the patient. The initial evaluation should include an appraisal of pain intensity, functional status, and quality of life, as

well as an assessment of known risk factors for potential harm, including history of substance use disorders and current substance use; presence of mood, stress, or anxiety disorders; medical comorbidity; and concurrent use of medications with potential drug–drug interactions. A redesign of the electronic health record may facilitate such an assessment, including integration of meaningful use criteria to increase its adoption. Finally, the incorporation of other clinical tools (such as prescription drug monitoring programs) into this assessment, although not well-studied, seems reasonable. Patient characteristics can be used to tailor the clinical approach, with those screening at highest risk for harm being triaged to more structured and higher-intensity monitoring approaches.

Treatment Options

Data to support the long-term use of opioids for chronic pain management are scant. Workshop speakers stressed the need to use treatment options that include a range of progressive approaches that might initially include nonpharmacologic options, such as physical therapy, behavioral therapy, and complementary and alternative medicine approaches with demonstrated efficacy, followed by pharmacologic options, including nonopioid pharmacotherapies. The use of and progression through these treatment methods would be guided by the patient's underlying disease state, pain, and risk profile as well as their clinical and functional status and progress. However, according to a workshop speaker, lack of knowledge or limited availability of these nonpharmacologic methods and the ready availability of pharmacologic options and the associated reimbursement structure seem to steer clinicians toward pharmacologic treatment, specifically opioids.

The type of pain could influence its management. Data were presented on 3 distinct pain mechanisms: peripheral nociceptive (caused by tissue damage or inflammation), peripheral neuropathic (caused by damage or dysfunction of peripheral nerves), and centralized (characterized by a disturbance in the processing of pain by the brain and spinal cord). Persons with more peripheral nociceptive pain (such as acute pain due to injury, rheumatoid arthritis, or cancer pain) may respond better to opioid analgesics. Those with central pain syndromes (for example, fibromyalgia, the irritable bowel syndrome, temporal-mandibular joint disease, and tension headache) respond better to centrally acting neuroactive compounds (such as certain antidepressant medications and anticonvulsants) than to opioids. According to a workshop speaker, evidence suggests that nonopioid interventions may better treat fibromyalgia and that patients with even a few signs of the disorder are at risk for poor response to opioids and a worse long-term course of pain. Speakers presented evidence that nearly all chronic pain may have a centralized component and suggested that opioids may promote progression from acute nociceptive pain to chronic centralized pain. However, several speakers and audience members cautioned against making blanket statements about who is or is not likely to benefit from opioids.

Clinical Management

Clinicians have little evidence to guide them once they make the decision to prescribe opioids for chronic pain therapy. Data on selecting specific agents on the basis of drug characteristics, dosing strategies, and titration or tapering of doses are insufficient to guide current clinical practice. Some clinicians may use opioid rotation, whereby they transition a patient from an existing opioid regimen to another with the goal of improving therapeutic outcomes. However, this approach has not been formally evaluated. The use of equianalgesic tables (opioid conversion tables), which provide a list of equianalgesic doses of various opioids to guide clinicians in determining doses when converting from one to another, was an issue of particular concern. The equianalgesic dose is a construct based on estimates of relative opioid potency. Many opioid conversion tables are available, and speakers noted the lack of consistency among them. Many studies that determined these equianalgesic doses were conducted in a sample of the study population and using data points that may not be generalizable to patients presenting with chronic pain. The FDA has begun including data obtained from drug trials and postmarketing studies in package inserts to aid clinicians in switching between opioids, but many clinicians and pharmacists seem to be unaware of this. Speakers discussed the concept of incomplete cross-tolerance, whereby providers may need to reduce the dose by 25% to 30% when converting between opioids. Because of its longer half-life, methadone may require a larger reduction (up to 90%).

Determination and Assessment of Outcomes

Patient assessments should be ongoing and should include both positive and negative outcomes. The range of items on such assessments might include pain intensity and pain frequency, using both a short time reference as well as a longer time frame for comparative purposes; functional status, including effect on functions of daily living; quality of life; depression; anxiety; potential misuse or abuse of opioid medications; potential adverse medical effects of opioids; and other measures that mimic items obtained during the initial clinical risk profiling. These frequent reassessments should guide maintenance or modification of the current treatment regimen, and patients who do not meet the mutually agreed-on clinical outcomes should be considered for discontinuation of opioid therapy. Although many speakers agreed on the need for an "exit strategy," there was less consensus and few data on how one should be implemented.

Adverse Events and Side Effects

Potential harms include the risk for an opioid-use disorder, increased risk for falls and fractures, hypogonadism with resultant sexual dysfunction, and myocardial infarction (1). Realistic expectations about potential harms from various treatment options should be discussed with patients as well as relatives and caregivers.

Communication options should be available to discuss evolving concerns; for example, adverse events and side effects might be monitored regularly and reported to the clinician between regularly scheduled visits by using the Internet or other communication channels.

Risk Mitigation Strategies

Data on the efficacy of risk mitigation strategies, such as patient agreements, urine drug screening, and pill counts, are lacking. Although some speakers expressed concern about the effectiveness of patient agreements, the use of such agreements and other care support mechanisms might be an option as part of a comprehensive care management plan. Naloxone, which has traditionally been used to reverse heroin overdose, was highlighted as a potential risk mitigation strategy for patients who are prescribed opioids for chronic pain.

Reducing the Next Generation of Long-Term Opioid Users

Speakers stated that a multidisciplinary team approach that emulates the functions of a multidisciplinary pain clinic would be desirable given the success of such models in treating the whole person and not merely the pain condition, which may not be a simple, single entity. The use of a more effective chronic disease care model based on a comprehensive biopsychosocial model of care may have implications for reducing the potential for a new generation of long-term opioid users.

Challenges Within the Health Care System

A major influence on opioid prescribing is the evolution of the larger health care system and the current state of primary care. Pain is a multidimensional problem ranging from discomfort to agony and affecting physical, emotional, and cognitive function as well as interpersonal relationships and social roles. Therefore, best practice models for chronic pain management require a multidisciplinary approach similar to that recommended for other chronic complex illnesses, such as depression, dementia, eating disorders, or diabetes. Unfortunately, team-based approaches to care for pain have largely been abandoned. Instead, management of chronic pain has primarily been relegated to primary care providers working in health systems not designed or equipped for chronic pain management. Primary care providers often face competing clinical priorities in patients with chronic pain because these patients often have multimorbidity and polypharmacy. Time-consuming but important clinical tasks, such as conducting multidimensional assessments, developing personalized care plans, and counseling, have given way to care processes that can be accomplished more quickly and with fewer resources, such as prescription writing and referrals. In the case of pain management, which often requires substantial face-to-face time, quicker alternatives have become the default option. As a result, providers often prescribe opioids for pain even when other methods might be safer and more effective. Moreover, most practices do not have access to experts in pain management, including specialty pain clinics, or alternative approaches to pain management.

Payment structures and incentives are also important system-level facilitators for excessive opioid use. Fee-for-service payment has traditionally focused on the processes of medical care rather than the outcomes of care valued by patients. Current reimbursement for evaluation and management may be inadequate to reflect the time and team-based approaches needed for integrative treatment. In some instances, payment structures place barriers to nonopioid therapy, such as formulary restrictions that require evidence of failure of multiple therapies before nonopioid alternatives (such as pregabalin) are covered. Other payment structures, such as tiered coverage systems, keep nonopioid alternatives as second- or third-line options rather than placing them more appropriately as first-line therapy. Other incentives encourage prescribing opioids for several months at a time rather than prescribing them for a shorter period or using lower-volume prescriptions.

Finally, fragmentation of care across multiple providers and sites often leads to patients receiving prescriptions from multiple providers. This may lead to inappropriate prescribing of not only opioids but also unsafe drug combinations, such as opioids and benzodiazepines. Up to 25% of patients with chronic pain receive their medications in the emergency department, thus often effectively bypassing the primary care system. Patients may consult multiple specialists with relevant expertise in chronic pain, but these specialists may prescribe opioids without the knowledge of primary care providers.

Research Methods and Measurement

The EPC report found that much of the available literature was of poor quality or was not readily applicable to treating patients with chronic pain with long-term opioid therapy (1). Research on chronic pain is complicated by the heterogeneity of definitions, patient characteristics (such as age, sex, and race/ethnicity), causes, clinical presentations that include various comorbid conditions, and available opioids for prescription. Some of the important methodological problems are discussed in the following sections.

Definitions

Extrapolating findings of studies examining the effects of opioids on acute pain to chronic pain is particularly difficult. One of the central definitional problems is defining acute versus chronic pain. Various durations are used to define the latter, including more than 3 months, more than 6 months, and an arbitrary duration. The American Academy of Pain Medicine suggests that chronic pain is best defined as pain that does not remit in the expected amount of time. This is clearly an individualized pain assessment, and although it may be

useful to the clinician, it is not a standard definition that could be used for research purposes. The panel noted that detectable changes in brain function occur as pain moves from acute to chronic states; however, although this may provide a more precise, functional definition of pain, it is unrealistic to expect that most research will incorporate methods that measure brain function.

Unclear definitions also impair the understanding of the types of pain that patients have. Many research studies compare patients with cancer pain and those with noncancer pain. This dichotomy is clearly insufficient because neither type is homogeneous. Moreover, chronic pain is heterogeneous and complex and is not easily partitioned into mutually exclusive, discrete categories. This definitional problem affects diagnosis, treatment, and drug regulation.

Definitions are important when one is considering how to measure outcomes. Pain relief is a major focus of treatment and research, but quantifying pain is difficult. The typically used scale of 0 to 10 provides an overall sense of pain but not an assessment of its components. For example, a workshop speaker mentioned that recent work on the concept of "fibromyalgianess" (the tendency to respond to illness and psychosocial stress with fatigue, widespread pain, a general increase in symptoms, and similar factors) identifies at least 3 components of chronic pain that are important to measure: chronic pain or irritation in specific body regions, somatic symptoms (such as fatigue, sleep, mood, and memory), and sensitivity to sensory stimuli.

Measurement

The EPC report found that standardized risk assessment tools lacked sufficient sensitivity and specificity to be clinically useful. In large part, the problem with screening is that it is not clear what risk factors should be measured or whether it is feasible or sensible to screen for risk. Some speakers indicated that clinicians should assume that all patients are at risk and not use valuable resources, including clinician time, to screen.

Various patient outcomes may be important. Many speakers indicated that the primary goal for researchers and clinicians may be reducing pain but that patients may be more interested in improving quality of life and function rather than absolute pain reduction. Key components of a thorough assessment of patient outcomes should include measures of pain, psychopathology, quality of life, social factors (such as days worked), safety, and adverse outcomes.

Research Design

There is a clear need for well-designed longitudinal studies of effectiveness and safety of long-term opioid use in the management of chronic pain. Such studies—because of their length and the heterogeneity of factors to be accounted for—would need to be large and would therefore be expensive. It is not clear from a practical standpoint that patients with chronic pain would be willing to be randomly assigned to placebo, nonpharmacologic treatments, or nonopioid medications. Alternative designs that involve enrolling patients receiving long-term treatment into a study and randomly assigning them to maintenance versus tapering of the opioid dose might be considered if enough persons who are willing to have their medication dose tapered could be recruited. Pragmatic designs with flexibility in the treatments used might lessen some of the challenges in conducting long-term trials. Several speakers suggested that longitudinal studies were more feasible than randomized trials. They also noted that using the electronic health record to track pain and markers of improvement as well as adverse outcomes and side effects may provide the best data on large populations. Some speakers noted limitations of FDA-mandated postmarketing surveillance studies by pharmaceutical companies but also saw them as an opportunity to gain valuable information.

The panel considered how best to account for heterogeneity across patients, medications, and outcomes and concluded that novel design and statistical approaches are needed to manage such complexity. For example, ecological designs should be considered that embrace heterogeneity and aim to understand diversity among patients and to identify key subgroups that may respond differently to various treatments. This methodology often incorporates novel statistical methods (such as latent class and profile analyses).

Final Panel Recommendations and Summary

The panel's major recommendations are presented in the Table. Comments about specific research issues that merit further exploration are in the full report (https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/opioids-chronic-pain/workshop-resources#finalreport).

The increase in the number of Americans with chronic pain and the concurrent increase in the use of opioids to treat this pain have created a situation in which large numbers of Americans are receiving suboptimal care. Patients who are in pain are often denied the most effective comprehensive treatments; conversely, many patients are inappropriately prescribed medications that may be ineffective or even harmful. At the root of the problem is the inadequate knowledge about the best approaches to treating various types of pain, which balance effectiveness with the potential for harm, as well as a dysfunctional health care delivery system that promotes prescription of the easiest rather than the best approach to addressing pain. The EPC report identified few studies that were able to answer key questions, which suggests a dire need for research on the effectiveness and safety of opioids as well as optimal management and risk mitigation strategies. Particularly striking to the panel was the realization that evidence is insufficient for every clinical decision that a provider needs to make about the use of opioids for chronic pain, leaving the provider to rely on his or her own clinical experience.

Because of the inherent difficulties of studying pain and the large number of patients already receiving opioids, new research designs and analytic methods are

Table. Panel Recommendations

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 randomized clinical trials.
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 health care 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 health care 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 to facilitate more consistent implementation of them in clinical care.

needed to adequately answer the important clinical and research questions. Until the needed research is conducted, health care delivery systems and clinicians must rely on the existing evidence as well as guidelines issued by professional societies. Systems of care must facilitate the implementation of these guidelines rather than relying solely on individual clinicians, who are often overburdened and have insufficient resources.

Opioids are clearly the best treatment for some patients with chronic pain, but there are probably more effective approaches for many others. The challenge is to identify the conditions in patients for which opioid use is most appropriate, the optimal regimens, the alternatives for those who are unlikely to benefit from opioids, and the best approach to ensuring that every patient's needs are met by a patient-centered health care system. For the more than 100 million Americans living with chronic pain, meeting this challenge cannot wait.

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Note: A list of the workshop panelists, speakers, working group members, and sponsors is provided in the **Appendix** (available at www.annals.org).

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Appendix: Workshop Panelists, Speakers, Working Group, and Sponsors

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