Introduction

Chronic pain affects an estimated 100 million Americans, or one-third of the U.S. population. In addition to the burden of suffering that accompanies pain, it is the primary reason that Americans are on disability. The societal costs of chronic pain are estimated at between $560 and $630 billion per year as a result of missed work days and medical expenses.

Although numerous treatments are available for treatment of chronic pain, workshop speakers presented data from numerous sources that indicate a dramatic increase in opioid prescriptions and use over the past 20 years. For example, the number of prescriptions for opioids written for pain treatment in 1991 was 76 million; in 2011, this number reached 219 million opioid prescriptions. This striking increase in opioid prescriptions has paralleled the increase in opioid overdoses and treatment admissions. In fact, treatment admissions for prescription painkillers have increased more than fivefold in the last two decades. Yet, evidence also indicates that
40 percent to 70 percent of individuals with chronic pain are not receiving proper medical treatment.

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 whether we, as a nation, are currently approaching chronic pain in the best possible manner that maximizes effectiveness and minimizes harm.

On September 29–30, 2014, the National Institutes of Health (NIH) convened a Pathways to Prevention Workshop: The Role of Opioids in the Treatment of Chronic Pain. Specifically, the workshop addressed four key questions:

1. What is the long-term effectiveness of opioids?
2. What are the safety and harms of opioids in patients with chronic pain?
3. What are the effects of different opioid management strategies?
4. What is the effectiveness of risk mitigation strategies for opioid treatment?

To answer these questions, the Pacific Northwest Evidence-based Practice Center, under contract to the Agency for Healthcare Research and Quality, completed a review of the literature related to these questions. The NIH conducted a 1½-day workshop featuring more than 20 speakers with various expertise and viewpoints. In addition, audience members expressed many other experiences and views during the discussion periods.
Context

To understand the problem of opioids and chronic pain, the panel felt strongly that an understanding of underlying contextual factors was crucial. Many workshop presentations provided information about these contextual factors, including background on the scope of patient pain and its treatment, the patient’s experience of pain and pain management, the current public health issues associated with treatment of pain, and the historical context that underlies the current use and overuse of opioids in the treatment of chronic pain.

As noted in the introduction, pain affects millions of Americans, and the societal costs are high. For patients, chronic pain is often associated with psychological distress, social disruptions, disability, and high medical expenses. In addition, chronic pain is on the rise as is opioid use. This use has been associated with pain relief, but also with an increase in adverse outcomes (e.g., addiction, overdose, insufficient pain relief).

Given the rise in chronic pain syndromes and the poor outcomes associated with opioid treatment, the panel felt it was fundamental to understand the patient’s perspective. At the workshop, the panel heard from individuals struggling with chronic pain and advocates for afflicted individuals about their experience. The burden of dealing with unremitting pain is devastating to the patient’s psychological well-being and can negatively affect a person’s ability to maintain gainful employment or achieve meaningful advancement professionally. It affects relationships with spouses and significant others and limits engagement with friends and other social activities. The prospect of living a lifetime with pain induces fear and demoralization and can lead to diagnoses of anxiety and depression.
Coupled with psychological and social effects are the negative encounters that many individuals with chronic pain experience with the health care system. Providers, often poorly trained in management of chronic pain, are quick to label patients as “drug-seeking” or as “addicts” who overestimate their pain. Some doctors “fire” patients for increasing their dose or merely for continuing to voice concerns about their pain management. Some patients have had similarly negative interactions with pharmacists. These experiences may make patients feel stigmatized, or labeled as criminals. These experiences heighten fears that pain-relieving medications will be “taken away,” leaving the patient in chronic, disabling pain. In addition, negative perceptions by clinicians can create a rupture in the therapeutic alliance, which some studies have identified as impeding successful opioid treatment. For example, cultural factors may influence the treatment a patient receives from health care providers. White providers tend to underestimate the pain of black patients and perceive them to be at higher risk than white patients for substance abuse.

Biased media reports on opioids also affect patients. Stories that focus on opioid misuse and fatalities related to opioid overdose increase anxiety and fear among some treated patients that their medications may be tapered or discontinued. For example, one workshop presentation indicated that a typical news story about opioids was likely to exclude information about the legitimate prescription use of opioids for pain, focusing instead on overdose, addiction, and criminal activity surrounding the use of opioids.

However, the panel also wants to emphasize what was reflected in numerous presentations at the workshop: Many patients have been compliant with their prescriptions and feel that their pain is managed adequately to the point of satisfactory quality of life. In addition, many physicians feel that opioid treatment can be valuable for some patients.
The patient perspective is incredibly important, and yet it is only one aspect of the problem. Another equally important consideration is how prescription opioids used in the treatment of chronic pain create public health problems. In other words, although some patients experience substantial pain relief from prescription opioids and do not suffer adverse effects, these benefits have to be weighed against problems caused by the vast number of opioids now prescribed.

Several workshop speakers indicated that 80 percent of all opioid prescriptions worldwide are written in the United States. This suggests, in part, that other countries have found different treatments for chronic pain. According to the Centers for Disease Control and Prevention, there were approximately 17,000 overdose deaths involving opioids in 2011. Different age groups are affected differently. For example, in 2010, one out of eight deaths of 25- to 34-year-olds was opioid-related (Gomes et al., 2014). There are also collateral deaths from those who have been prescribed opioids. In a 3-year period (2003 to 2006), more than 9,000 children were exposed to opioids. Of these, nearly all children ingested the opioid (99 percent) and the ingestion occurred in the home (92 percent). A small number of children died (n=8), but 43 children suffered major effects, and 214 suffered moderate effects (Bailey, 2008). Neonatal narcotic withdrawal also has increased, with an estimated 29,000 infants affected. Both short-term physiological problems as well as long-term behavioral consequences result from this withdrawal. (Bada, U of KY)

There is some concern that opioids are now becoming gateway drugs for heroin use. For example, Cicero (2014) found that among individuals with a heroin addiction in the 1960s, the first opioid used (the entry drug into heroin) was heroin itself. However, by the year 2000, the entry drug to heroin use was an opioid.
Speakers at the workshop expressed almost unanimous concern that physicians are unable to
distinguish among individuals who would use opioids for pain management, those who would
use them for pain management and then become addicted, and those who use because of primary
substance use disorders. For example, in one study of individuals treated for chronic pain, the
addiction prevalence, depending on criteria, ranged from about 14 percent to about 19 percent
(Højsted et al., 2010).

Finally, there is a major public health concern 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 people age 12 and older abusing analgesics,
53 percent reported receiving them for free from a friend or relative. Only 23.8 percent received
prescriptions from one or more doctors.

Another key contextual factor the panel considered was a historical perspective. The panel
identified important historical factors related to approval by the U.S. Food and Drug
Administration (FDA) of opioid medications, introduction of new opioid medications
(particularly extended-release formulations), training of prescribers, and health system changes.

Different opioids have undergone varying levels of scrutiny by the FDA. All current, extended-
release opioids have been approved for acute and chronic pain based on 12-week adequate and
well-controlled efficacy studies. A number of immediate-release opioids had been on the market
without prior approval; however, in recent years, all of them have received FDA approval for
acute pain. In other words, the FDA has approved these drugs for long-term use, but they have
not been evaluated for safety and efficacy for longer than 12 weeks.
The introduction of new opioid drugs on the market over the past decade, particularly those with extended-release formulations, made them attractive to patients and clinicians who perceived them as safe and effective. There were no long-term studies on which to base clinical decisions. Physicians had little training in how to manage chronic pain patients and did not have to demonstrate knowledge in how to prescribe these medications in order to be licensed to prescribe.

Changes in the health care system have provided perverse incentives for clinicians to prescribe opioids in the brief amount of time they have with patients. There is little reimbursement for models of care that include a chronic care management team and ancillary services, despite the evidence base that these are the most effective approaches to chronic pain management. As a result, the burden of care management frequently falls on the individual clinician, in particular the primary care physician. With an average of 15 or 20 minutes per visit, the most expeditious way to manage pain while also attending to other medical conditions is to prescribe an opioid.

Of course, the historical and current context of opioid use and prescription is complicated by the heterogeneity of the problem. There are many facets of heterogeneity: patients (e.g., age, gender, race); the pain etiology (e.g., peripheral vs. central pain), diverse clinical presentations that include various comorbidities; characteristics of the clinical setting (e.g., providers, payment structures); and the available opioids for prescription (e.g., differential receptor affinities, pharmacokinetics, potential for drug interactions).

Given these complexities, the panel struggled with how to settle the conundrum of striking a balance between two ethical principles: beneficence and doing no harm. Specifically, the balance was between 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 are essential to move the field of chronic pain management forward. However, one of the central struggles the panel grappled with in making recommendations is the dearth of empirical evidence to support the four key questions addressed by the Evidence-based Practice Center (EPC) report. Thus, in order to make recommendations in this report, the panel synthesized both evidence from the EPC report and presentations that focused on clinical experience as well as smaller trials and cohort studies (e.g., non-randomized clinical trials).

Clinical Issues

Patient Assessment and Triage

Chronic pain is a complex clinical issue requiring an individualized, multifaceted approach. Contributing to the complexity is the fact that chronic pain is not limited to a particular disease state but rather spans a multitude of conditions, with varied etiologies and presentations. Yet, traditionally, persons living with chronic pain often have been grouped or “lumped” into a single category, and treatment approaches have been generalized with little evidence to support this practice. In addition, although pain is a dynamic phenomenon, waxing and waning and changing in nature over time, it is often viewed and managed with a static approach. For a number of reasons—including lack of knowledge, practice setting, resource availability, and reimbursement structure—clinicians are often ill-prepared to diagnose, appropriately assess, treat, and monitor patients with chronic pain. Based on the evidence report and the workshop presentations, the panel has identified several clinical management issues worthy of further discussion.
First, there must be recognition that patients’ manifestation of and response to pain is varied, with genetic, cultural, and psychosocial factors all contributing to this variation. Evidence was presented that clinicians’ response to patients with pain also differs, often resulting from preconceived notions and biases based on racial, ethnic, and other sociodemographic stereotypes. The totality of the data points to the need for an individualized, patient-centered approach based on a biopsychosocial model as opposed to the biomedical model that is more commonly employed. Treating pain and reducing suffering do not always equate, and many times patients and clinicians have disparate ideas on successful outcomes. A more holistic approach to the management of chronic pain, inclusive of the patients’ perspectives and desired outcomes, should be the goal.

Patients, providers, and advocates all agree there is a subset of patients for whom opioids are an effective treatment method for their chronic pain, and limiting or denying access to opioids for these patients can be harmful. It appears that these patients can be safely monitored using a minimally structured approach, which includes optimization of opioid therapy, management of adverse effects, and brief follow-up visits at regular intervals. Therefore, recommendations regarding the clinical use of opioids should avoid harm in patients currently benefiting from this treatment.

This concept that some patients benefit while others may receive no benefit or in fact may be harmed highlights the current challenges of appropriate patient selection. Data are limited on effective risk prediction instruments for identifying patients at highest risk for the development of adverse outcomes (e.g., overdose, development of an opioid use disorder). Yet, longitudinal studies have demonstrated risk factors (e.g., substance use disorders, other comorbid psychiatric illnesses) that are more likely to be associated with these harmful outcomes. Ideally, patients
with these risk factors would be less likely to receive opioids or more likely to receive them in
the context of a maximally structured approach; however, studies of large clinical databases
suggest the opposite. Although the literature to support use of specific risk assessment tools is
insufficient, the consensus appears to be that the approach to the management of chronic pain
should be individualized, based on a comprehensive clinical assessment that is conducted with
dignity and respect, without value judgments or stigmatization of the patient. Based on the
workshop presentations, this initial evaluation would include an appraisal of pain intensity,
functional status, and quality of life, as well as 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. Additionally, there may be a role for the redesign of the
electronic health record to facilitate such an assessment, including integration of meaningful use
criteria to increase its adoption. Finally, incorporating the use of other clinical tools
(e.g., prescription drug monitoring programs) into this assessment, although not well studied,
seems to be widely agreed upon. These factors also can be used to tailor the clinical approach,
triaging those screening at highest risk for harm to more structured and higher intensity
monitoring approaches.

Treatment Options

Despite what is commonly done in current clinical practice, there appear to be few data to
support the long-term use of opioids for chronic pain management. Several workshop speakers
stressed the need to use treatment options that include a reasonable range of progressive sets of
approaches that might initially include nonpharmacological options, such as physical therapy,
behavioral therapy, and/or proven complementary and alternative medicine approaches with
demonstrated efficacy, followed by pharmacological options, including non-opioid pharmacotherapies. The use of and progression through these treatment modalities 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 nonpharmacological modalities and the readily availability of pharmacological options and associated reimbursement structure appear to move clinicians to the use of pharmacological treatment choices and, more specifically, opioids.

One area of clinical importance the panel reviewed was the notion that pain type could influence pain management. Data were presented on three distinct pain mechanisms: (1) peripheral nociceptive—caused by tissue damage or inflammation, (2) peripheral neuropathic—damage or dysfunction of peripheral nerves, and (3) centralized—characterized by a disturbance in the processing of pain by the brain and spinal cord. Individuals with more peripheral/nociceptive types of pain (e.g., acute pain due to injury, osteoarthritis, rheumatoid arthritis, cancer pain) may respond better to opioid analgesics. In contrast, those with central pain syndromes—exemplified by fibromyalgia, irritable bowel syndrome, temporal-mandibular joint disease and tension headache—do not respond as well to opioids, but rather to centrally acting neuroactive compounds (e.g., certain antidepressant medications, anticonvulsants). In particular, there is strong evidence for non-opioid interventions in treatment of fibromyalgia, one of the most common conditions presenting in primary care and pain clinics. In fact, the workshop presented interesting preliminary evidence that if an initial evaluation for pain demonstrated even a few signs of fibromyalgia (not meeting criteria for the full syndrome), the patient was at risk for poor response to opioids and a worse long-term course of pain. In addition, speakers presented evidence that nearly all chronic pain may have a centralized component and it was 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, again highlighting the importance of individualized patient assessment and management. The health care system would benefit from additional research on these different mechanisms of pain and the optimal approaches for each, identifying risk factors for patients most likely to develop chronic pain after an acute or subacute pain syndrome as well as ways to mitigate or reduce the risk of transitioning to a chronic pain syndrome.

Clinical Management

There is little evidence to guide a clinician once they have made the decision to initiate opioids for chronic pain therapy. Data on selection of specific agents based on opioid characteristics, dosing strategies, and titration or tapering of opioids are insufficient to guide current clinical practice. Discussed during the workshop was the concept of opioid rotation in which one changes from an existing opioid regimen to another with the goal of improving therapeutic outcomes. The use of equianalgesic tables (opioid conversion tables), which provide a list of equianalgesic doses of various opioids to guide clinicians in determining doses for converting from one opioid to another, was an issue of particular concern. The equianalgesic dose is a construct based on estimates of relative opioid potency. A multitude of these opioid conversion tables are available in both the peer-reviewed and non-peer-reviewed literature, and speakers noted the lack of consistency between the tables. Many of the studies to determine these equianalgesic doses were conducted in study samples and using data points that may not generalize to patients presenting with chronic pain. The FDA has begun including data obtained from drug trials and post-marketing studies in package inserts to aid clinicians in switching
between opioids, but it appears that many clinicians and pharmacists are not aware of this.

Furthermore, although three known classes of opioid receptors—μ (μ), κ (κ), and δ (Δ)—have been identified, multiple receptor subtypes within each of these classes in fact can alter the effect of opioids based on receptor subtype binding. This led to a discussion between workshop speakers of the concept of incomplete cross-tolerance, in which providers may need to reduce the dose by 25 to 30 percent when converting between one opioid and another. Because of its longer half-life, methadone may require a larger reduction (up to 90 percent); in fact, the speakers argued that methadone should be excluded from these tables. They suggested that the use of these tables may have led to harm and should not be broadly used, and there was a call for the development of validated and patient-specific types of equianalgesic tables. The majority of clinicians receive little to no education on use of and converting from one opioid regimen to another, and this should be a focus of future clinical education and clinical decision support efforts.

Determination and Assessment of Outcomes

Several workshop speakers noted that patient assessments should be ongoing, including both positive and negative outcomes. The range of items on assessments might include pain intensity and pain frequency, using both a short time reference as well as a longer timeframe for comparative purposes, functional status including impact on functions of daily living, quality of life, depression, anxiety, and other measures that mimic those items obtained during the initial clinical risk profiling. These frequent reassessments should guide maintenance or modification of the current treatment regimen, and patients who are failing to meet the mutually agreed upon clinical outcomes should be considered for discontinuation of opioid therapy. Although there
appears to be consensus among speakers on the need for an “exit strategy,” there was less
consensus and very few data on how one should be implemented.

Adverse Events and Side Effects

In addition to the very real risk of development of an opioid use disorder, chronic administration
of opioids are associated with other adverse effects, including increased risk of falls and
fractures, hypogonadism with resultant sexual dysfunction, and, in at least two studies, increased
risk of myocardial infarction. These factors are important to the discussion of risks versus
benefits with patients, and realistic expectations regarding adverse events and side effects from
various treatment options may need to be explained to patients as well as relatives and home care
providers. Improved patient communication options may be of value for the patients or relatives
to discuss evolving concerns. Adverse events and side effects might be monitored regularly and
reported to the clinician between regularly scheduled visits using web or other communication
channels.

Risk Mitigation Strategies

As with much of the other data on opioid use for chronic pain, data are limited on the efficacy of
various risk mitigation strategies, including patient agreements, urine drug screening, and pill
counts. Some speakers expressed concern as to the effectiveness of patient agreements as few
data are available to support their use. However, the use of patient agreements and other care
support mechanisms might be an option as part of a comprehensive care management plan and
be reinforced without the use of judgmental perspectives that could impact the relationship
between patient and provider. Naloxone, which traditionally has been used to reverse heroin
overdose, was highlighted as a potential risk mitigation strategy for patients who are prescribed
opioids for chronic pain. Guided by the premise that these are risky drugs as opposed to risky
patients, a workshop speaker suggested that naloxone might be provided to patients at the same
time as the original prescription for the opioid and that this might provide an opportunity for
additional patient education. Other speakers were more cautious about using this strategy for all
patients, yet were willing to consider that it might be explored from an individual patient risk
benefit perspective.

Reducing Next Generation of Chronic Opioid Users

It was stated that a multidisciplinary team approach that emulates the functions of a
multidisciplinary pain clinic would be desirable given the prior history of success of such models
in treating the whole person and not merely the pain condition, which may not be a simple,
single entity. As noted above, different types of pain—peripheral noxious, peripheral
neuropathic, and centralized pain—appear to have different response profiles for such
treatments. Furthermore, the use of a more effective chronic disease care model may have
implications for reducing the potential of a new generation of chronic opioid users as the
continued first-line use of opioids for chronic pain treatment is generally suboptimal and has the
potential for addiction. Although the team composition may vary, members might include the
primary care provider, case or care managers, nurses, pharmacists, psychologists, psychiatrists,
social workers, and other pain specialists. However, the current health care priorities do not
appear to bode well for the re-initiation of such an approach. Finally, one simple approach the
panel considered to decrease the conversion of acute users to chronic users was to advise those
prescribing opioid medications for the treatment of acute pain (e.g., in the post-operative setting
or for an injury) to prescribe fewer pills to be taken over a shorter but clinically reasonable
timeframe, as there is some evidence that higher numbers of pills initially prescribed is related to risk of chronicity of use.

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. The panel heard reports of major problems with the current health care system, including:

- Poor support for team-based care and specialty pain clinics
- Over-burdened primary care providers
- A lack of knowledge and decision support for chronic pain management
- Financial misalignment favoring the use of medications
- Fragmentation of care across different providers.

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. As with other chronic conditions, chronic pain management requires a more comprehensive biopsychosocial model of care. 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. Research demonstrates that these conditions can be managed successfully using an interdisciplinary team-based approach to care (e.g., medicine, psychology, nursing, pharmacy, social work). Early efforts to manage pain in the late 20th century were based on similar effective models of interdisciplinary, comprehensive, and individualized care. Unfortunately, as health care systems evolved and
increasingly implemented and maintained only those interventions that were declared to be revenue-generating, team-based approaches to care for pain were largely abandoned. Instead, management of chronic pain has been largely relegated to the primary care providers working in health systems not designed or equipped for chronic pain management. Moreover, expectations for primary care providers increasingly evolved to productivity-based metrics, with more tasks to be completed within a 10- to 20-minute office visit. Primary care providers often face competing clinical priorities in patients with chronic pain because these patients often have multi-morbidity and polypharmacy. Administrative responsibilities also compete for the provider’s time. For example, growing requirements for documentation in the electronic health record are consuming a larger portion of the office visit. Hence, 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 quicker and with fewer resources, such as prescription writing and referrals. In the case of pain management, which often takes substantial face-to-face time, quicker alternatives have become the default option. As a result, providers often prescribe opioids for pain even when, for any given patient, the pain might be treated more safely and effectively with other modalities. Primary care providers are charged with relieving pain as a professional obligation and a fundamental goal of health care. However, these providers have often received little specific training in chronic pain management or in the use and management of opioids. This may be particularly true for those providers who were trained before newer formulations of opioids or other alternatives were available. As the systematic review clearly reveals, these providers do not have access to evidence-based dosing schedules, adjustment and switching rules, or tapering and stopping rules to guide pain management. Even if primary care providers had the requisite
knowledge, skill, and intent, they often do not have access to the resources needed to manage pain according to current guidelines. This is often true because alternative first-line treatment strategies are not available. For example, most practices do not have access to experts in pain management, including specialty pain clinics or access to the alternative approaches to pain management (e.g., physical therapy, cognitive and behavioral approaches, acupuncture, yoga, meditation, other complementary and alternative medicine). Therefore, clinicians provide a prescription for opioids because they and their patients feel it is the only or the most expedient alternative. Once the decision to initiate opioids has been made, patients and providers lack practical tools to monitor the outcomes of chronic pain management. For example, simple monitoring tools (e.g., the Patient Health Questionnaire-9 for depression) assist in the diagnosis and management of depression. Although widely available, pain rating scales alone are not comprehensive enough to measure the adequacy of pain control on important dimensions such as quality of life, function, and employment.

Payment structures and incentives also represent an important system-level facilitator for excessive opioid use. Fee-for-service payment traditionally has not focused on the outcomes of care valued by patients, but rather on the processes of medical care. 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 non-opioid therapy, such as formulary restrictions that require failure of multiple therapies before covering non-opioid alternatives (e.g., pregabalin). Other payment structures, such as tiered coverage systems, place non-opioid alternatives as second- or third-line options rather than their more appropriate placement as first-line therapy. Other incentives encourage prescribing opioids for several months at a time rather than for a shorter term or lower volume prescriptions because
providers are instructed that patient and administrative costs are lower and convenience is improved with longer and larger volume prescriptions. The panel heard reports that this apparently benign incentive actually may lead to increased risk of opioid dependence or other adverse events, including harm through nonmedical uses. Moreover, current reimbursement policies do not provide payment for some of the health professionals who are needed to provide best practice pain management (e.g., pharmacists, care coordinators). In health systems that are primarily fee-for-services, there may be incentives to generate short-term revenue, whereas in capitated systems, where physicians receive a set amount for each enrolled person per period of time, there may be greater incentive to invest in upfront resources (e.g., team-based care) if they can prevent downstream utilization (e.g., hospitalization). Given the current vagaries of payment structures, perhaps it is not surprising that providers and patients chose opioids more than is clinically appropriate and more often than guidelines suggest.

Finally, fragmentation of care across multiple providers and sites of care often leads to patients receiving prescriptions from multiple providers. This may lead not only to inappropriate prescribing of opioids but also to inappropriate prescribing of unsafe combinations of drugs such as opioids and benzodiazepines. Up to 25 percent of patients who have chronic pain receive their medications in the emergency department, often effectively bypassing the primary care system. Patients with chronic pain may see multiple specialists with relevant expertise in chronic pain (e.g., neurologists, orthopedists, rheumatologists, psychiatrists), but these specialists may often prescribe opioids without the knowledge of primary care providers. The specialists may focus on pain in isolation and may not recognize or consider the patient’s comorbid conditions, concomitant medications, or goals of care. Patients may actively “shop” for providers (within or across health care systems or state lines) to find a provider who is willing to prescribe opioids.
The panel heard recommendations that there is a clear need to address these system-level problems. Chief among these recommendations is the need to develop, evaluate, and implement new models of care for chronic pain management. To accomplish this fundamental goal, research must address health care aims and thus assess the costs and benefits to individuals and populations. Moving to team-based care is unlikely to happen without restructuring reimbursement systems, building patient-centered clinical information systems, expanding the roles and responsibilities of health care professionals beyond the physician, and new basic research on which patients require which care in which settings.

Methods and Measurement

Reliable and valid clinical and research methods are essential as the medical field seeks to understand best practices for chronic pain management. The EPC report found few long-term (more than 1 year) studies of opioid treatment, and those identified in the literature were typically of poor quality (see Summary of Findings Table). It is particularly difficult to extrapolate from studies examining the effects of opioids on acute pain to chronic pain. The panel identified methodological problems related to definitions, measurement, and research design.

Definitions. One of the central definitional problems is defining acute versus chronic pain. Various markers are used to define chronic pain, including lasting more than 3 months or lasting more than 6 months, leaving a time-based definition somewhat arbitrary. 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 individual clinician, does not provide a standard definition that could be
used for research purposes. The panel suggested that 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 the average research study will incorporate neuroimaging modalities.

Unclear definitions also impair understanding of the types of pain that patients experience. Many research studies compare patients with cancer-derived and non-cancer-derived pain. This dichotomy is clearly insufficient as neither cancer pain nor non-cancer pain are homogeneous, in large part because individual differences in sensory processing and augmented pain affect pain states. In other words, chronic pain is heterogeneous and complex. One workshop presentation focused on a contemporary view that indicates pain derives from three sources. Peripheral (nociceptive) pain, which typically involves tissue damage or inflammation; peripheral (non-nociceptive) pain, which involves damage of peripheral nerves; and centralized pain, which involves spinal or supraspinal mechanisms. However, although this rubric may be useful for considerations of acute pain, chronic pain should not be partitioned into mutually exclusive, discrete categories. This definitional problem affects diagnosis, treatment, and drug regulation.

Finally, definitions are important when considering how to measure outcomes. Pain relief is a major focus of treatment and research. However, it is difficult to quantify what pain is. The typically used 0–10 pain scale provides an overall sense of pain, but not an assessment of individual components related to pain. For example, recent work on the concept of “fibromyalgianess” (the tendency to respond to illness and psychosocial stress with fatigue, widespread pain, general increase in symptoms, and similar factors) identifies at least three components to chronic pain that are important to measure: chronic pain or irritation in specific
body regions, somatic symptoms (e.g., fatigue, sleep, mood, memory), and sensitivity to sensory stimuli.

**Measurement.** Research also suffers from significant measurement problems. Risk screening instruments would help clinicians implement better risk management strategies. Many speakers at the workshop indicated that the field does not have good risk assessment tools. For example, the commonly used 0–10 pain scale to screen for pain intensity may not be adequate and may not have good psychometric properties. The EPC report found that standardized tools lacked sufficient sensitivity and specificity to make them 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.

Finally, patient outcomes (typically measured in an ongoing manner) are important. Numerous speakers indicated that the primary goal for researchers and clinicians may be reduction in patient pain; however, patients may be more interested in improving quality of life, rather than absolute pain reduction. Functional behavior related to pain also needs to be assessed.

The most important aspect of measuring patient outcomes is to acknowledge that they are determined by multiple factors and therefore will need to be multidimensional in scope. Key components of a thorough assessment of patient outcomes would include measures of pain, psychopathology, quality of life, social factors (e.g., days worked), safety, and adverse outcomes.

**Research Design.** The panel reviewed several presentations related to study design. Based on the EPC report, 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; this is an immediate concern.
Such studies—both because of their length and the heterogeneity of factors to be accounted for—would need to be large and therefore expensive. In addition, it is not clear from a practical standpoint that patients with chronic pain would be willing to be randomized to placebo, nonpharmacological treatments, or non-opioid medications. The workshop speakers also proposed an alternative design, which involved accepting patients on long-term treatment into a study and randomizing them to maintenance versus tapering of the opioid. However, speakers noted similar practical issues around recruitment of individuals willing to have their medication tapered.

With these limitations, workshop speakers suggested other types of longitudinal studies; for example, an approach using a small cohort study was seen as a more feasible option. Also from a feasibility standpoint, the use of 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. In addition, some speakers noted limitations of FDA-mandated post-marketing surveillance studies by pharmaceutical companies, but also saw this as an opportunity to gain valuable information in this area.

Another design issue considered by the panel related to how best to account for heterogeneity across patients, medications, and outcomes. Novel design and statistical approaches may be needed to manage this complexity. For example, ecological designs that embrace heterogeneity and help to understand diversity among patients and to identify key subgroups that may respond differently to various treatments should be considered. This methodology often incorporates novel statistical methods (e.g., latent class and profile analyses).
The panel also noted several specific methodological issues that merit further exploration. These include the following:

1. Better understanding is needed of the window between effective dose and dose at which side effects and adverse outcomes occur. These may include studies on how this window is defined and assessed as well as the drug-related, genetic, and other patient-related factors that might affect the targeted dose range.

2. In adverse outcomes research, it is important to determine how best to model more immediate versus longer term side effects based on length of exposure to opioids. The notion was presented that some poor outcomes (e.g., falls) might be more associated with earlier treatment, whereas others (e.g., hypogonadism) might be more associated with longer term exposure. Future studies will need to encompass this time-varying aspect of certain adverse effects and poor outcomes.

3. Few studies have looked at genetic predictors of response and poor outcomes. There are several promising areas and specific loci for genetic research in this area, including a panel of gene variants related to cytochrome P450 metabolism (e.g., examining outcomes in people who are slow, intermediate, or fast drug metabolizers), receptor target single nucleotide polymorphisms (SNPs) as well as SNPs related to indirect modulation (e.g., COMT, the gene coding for catechol-O-methyltransferase), the drug transporter (e.g., ABCB1), and other polymorphisms derived from genome-wide association studies (e.g., rs2952768).

Incorporation of biological approaches will be important to understand etiology of chronic pain and the mechanisms involved with opiate response and poor outcomes. Greater incorporation of
functional imaging studies of pain as well as findings from clinical neuroscience on salient psychological factors hold promise for identifying patients who would best respond to opioids versus other pharmacological or nonpharmacological modalities. Finally, future studies might examine the utility of variables such as evoked pain sensitivity and endogenous opioid activity.

Implementation science may be useful to address some of the feasibility issues. For example, research on how to bring prescription monitoring systems into an electronic health record may be particularly important. Finding ways to incorporate pharmacists and nurses in care groups is also essential. A final example includes research into the cost-effectiveness of chronic pain management teams, particularly given anticipated incentives for pay for performance.

**Complementary Efforts**

As the medical community looks to ways for increasing available options to control pain and suffering, many complementary groups are at work. A report by the Institute of Medicine, *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, has sparked efforts from various agencies to partner in addressing this issue.

The NIH Pain Consortium has selected 12 health professional schools as Centers of Excellence in Pain Education (CoEPEs). The CoEPEs will act as hubs for the development, evaluation, and distribution of pain management curriculum resources for medical, dental, nursing, and pharmacy schools to enhance and improve how health care professionals are taught about pain and its treatment.

The Stanford-NIH Pain Registry, now called the National Collaborative Health Outcomes Information Registry (CHOIR) system provides clinicians with valuable information regarding
treatment outcomes. This platform collects outcomes data on large numbers of patients suffering from chronic pain.

The Interagency Pain Research Coordinating Committee is a federal advisory committee charged with coordination of all pain research efforts across all federal agencies. The ultimate goal of the committee is to advance the fundamental understanding of pain and to improve pain-related treatment strategies.

The FDA has recognized that extended-release and long-acting opioids are associated with serious risks. The FDA is now requiring additional studies and clinical trials to assess these risks, which include misuse, abuse, hyperalgesia, addiction, overdose, and death.

Many professional societies have taken a stance on the use of opioids for chronic pain. The American Academy of Neurology recently published a position paper on non-cancer pain. Initiatives such as the American Board of Internal Medicine’s “Choosing Wisely” have been under way.

Summary of EPC Report Findings

1. Effectiveness and comparative effectiveness

   a. In patients with chronic pain, what is the effectiveness of long-term opioid therapy for long-term (>1 year) outcomes related to pain, function, and quality of life?

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Strength of Evidence</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain, function, quality of life</td>
<td>Insufficient</td>
<td>No study of opioid therapy versus placebo or no opioid therapy evaluated long-term (&gt;1 year) outcomes related to pain, function, or quality of life.</td>
</tr>
</tbody>
</table>
2. Harms and adverse events

a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on (1) opioid abuse, addiction, and related outcomes; (2) overdose; and (3) other harms?

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Strength of Evidence</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abuse, addiction</td>
<td>Low</td>
<td>No randomized trial was evaluated. One retrospective cohort study found prescribed long-term opioid use associated with significantly increased risk of abuse or dependence versus no opioid use.</td>
</tr>
<tr>
<td>Abuse, addiction</td>
<td>Insufficient</td>
<td>In 10 uncontrolled studies, estimates of opioid abuse, addiction, and related outcomes varied substantially even after stratification by clinic setting.</td>
</tr>
<tr>
<td>Overdose</td>
<td>Low</td>
<td>Current opioid use was associated with increased risk of any overdose events (adjusted HR 5.2, 95% CI 2.1 to 12) and serious overdose events (adjusted HR 8.4, 95% CI 2.5 to 28) versus current nonuse.</td>
</tr>
<tr>
<td>Fractures</td>
<td>Low</td>
<td>Opioid use was associated with increased risk of fracture in one cohort study (adjusted HR 1.28, 95% CI 0.99 to 1.64) and one case-control study (adjusted OR 1.27, 95% CI 1.21 to 1.33).</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Low</td>
<td>Current opioid use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95% CI 1.19 to 1.37 and incidence rate ratio 2.66, 95% CI 2.30 to 3.08).</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Low</td>
<td>Long-term opioid use was associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI 1.1 to 1.9).</td>
</tr>
</tbody>
</table>
**b. How do harms vary depending on the dose of opioids used?**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Abuse, addiction</td>
<td>Low</td>
<td>One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared to no opioid prescription, the adjusted odds ratios were 15 (95% CI 10 to 21) for 1-36 MED/day, 29 (95% CI 20 to 41) for 36-120 MED/day, and 122 (95% CI 73 to 205) for ≥120 MED/day.</td>
</tr>
<tr>
<td>Overdose</td>
<td>Low</td>
<td>Versus 1 to 19 mg MED/day, one cohort study found an adjusted HR for an overdose event of 1.44 (95% CI 0.57 to 3.62) for 20 to 49 mg MED/day that increased to 11.18 (95% CI 4.80 to 26.03) at &gt;100 mg MED/day; one case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI 0.94 to 1.84) for 20 to 49 mg MED/day that increased to 2.88 (95% CI 1.79 to 4.63) at ≥200 mg MED/day.</td>
</tr>
<tr>
<td>Fracture</td>
<td>Low</td>
<td>Risk of fracture increased from an adjusted HR of 1.20 (95% CI 0.92 to 1.56) at 1 to &lt;20 mg MED/day to 2.00 (95% CI 1.24 to 3.24) at ≥50 mg MED/day; the trend was of borderline statistical significance.</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Low</td>
<td>Relative to a cumulative dose of 0 to 1350 mg MED over 90 days, the incidence rate ratio for myocardial infarction for 1350 to &lt;2700 mg was 1.21 (95% CI 1.02 to 1.45), for 2700 to &lt;8100 mg was 1.42 (95% CI 1.21 to 1.67), for 8100 to &lt;18,000 mg was 1.89 (95% CI 1.54 to 2.33), and for &gt;18,000 mg was 1.73 (95% CI 1.32 to 2.26).</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>Low</td>
<td>No association was found between opioid dose and risk of motor vehicle accidents.</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Low</td>
<td>Relative to 0 to &lt;20 mg MED/day, the adjusted OR for daily opioid dose of ≥120 mg MED/day for use of medications for erectile dysfunction or testosterone replacement was 1.6 (95% CI 1.0 to 2.4).</td>
</tr>
</tbody>
</table>
3. Dosing strategies

a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes and risk?

<table>
<thead>
<tr>
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<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Insufficient</td>
<td>Evidence from three trials on effects of titration with immediate-release versus sustained-release opioids reported inconsistent results on outcomes related to pain.</td>
</tr>
</tbody>
</table>

b. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life as well as the risk of overdose, addiction, abuse, or misuse?

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Pain and function</td>
<td>Low</td>
<td>No difference was found between various long-acting opioids.</td>
</tr>
<tr>
<td>Assessment of risk of overdose, addiction, abuse, or misuse</td>
<td>Insufficient</td>
<td>No studies were designed to assess risk of overdose, addiction, abuse, or misuse.</td>
</tr>
<tr>
<td>Overdose (as indicated by all-cause mortality)</td>
<td>Low</td>
<td>One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity adjusted analysis.</td>
</tr>
<tr>
<td>Abuse and related outcomes</td>
<td>Insufficient</td>
<td>One cohort study found some differences between long-acting opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions.</td>
</tr>
</tbody>
</table>
f. In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?

<table>
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</thead>
<tbody>
<tr>
<td>Pain, function, withdrawal due to opioid misuse</td>
<td>Low</td>
<td>No difference was found between more liberal dose escalation versus maintenance of current doses in pain, function, or risk of withdrawal due to opioid misuse, but there was limited separation in opioid doses between groups (52 vs. 40 mg MED/day at the end of the trial).</td>
</tr>
</tbody>
</table>

h. In patients on long-term opioid therapy, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?

<table>
<thead>
<tr>
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<th>Strength of Evidence</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Moderate</td>
<td>Two randomized trials found buccal fentanyl more effective than placebo for treating acute exacerbations of pain, and three randomized trials found buccal fentanyl or intranasal fentanyl more effective than oral opioids for treating acute exacerbations of pain in patients on long-term opioid therapy.</td>
</tr>
</tbody>
</table>
i. In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?

### Key Question

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Insufficient</td>
<td>Abrupt cessation of morphine was associated with increased pain and decreased function compared to continuation of morphine.</td>
</tr>
</tbody>
</table>

j. 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?

### Key Question

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Insufficient</td>
<td>No clear differences were found between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3 to 6 months.</td>
</tr>
</tbody>
</table>

### 4. Risk assessment and risk mitigation strategies

a. In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse?

### Key Question

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Insufficient</td>
<td>Based on a cutoff of &gt;4, three studies (all poor quality) reported very inconsistent estimates of diagnostic accuracy, precluding reliable conclusions.</td>
</tr>
<tr>
<td>Low</td>
<td>Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity of 0.38 in one study, for a PLR of 1.11 and NLR of 0.83. Based on a cutoff score of &gt;6, sensitivity was 0.73 in one study.</td>
</tr>
</tbody>
</table>
b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse?

<table>
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<tr>
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<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes related to abuse</td>
<td>Insufficient</td>
<td>No study evaluated the effectiveness of risk prediction instruments for reducing outcomes related to overdose, addiction, abuse, or misuse.</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval, HR=hazard ratio, MED=morphine equivalent dose, mg=milligrams, NLR=negative likelihood ratio, OR=odds ratio, PLR=positive likelihood ratio

As can be seen in the above table, the EPC found a paucity of studies on the long-term (more than 1 year) outcomes of opioid treatment for chronic pain and those identified in the literature were typically of poor quality. Further, there are insufficient data to guide appropriate patient assessment, opioid selection, dosing strategies, or risk mitigation. This underscores the need for high-quality research that focuses on establishing the appropriateness of long-term opioid treatment for the management of chronic pain. After listening to workshop speakers and audience members and examining the limited availability of studies on long-term opioid treatment, the panel makes following recommendations:

**Recommendations**

1. Federal and non-federal agencies should sponsor research to identify which types of pain, specific diseases, and patients are most likely to benefit from opioids.
2. Federal and non-federal agencies should sponsor research to identify which types of pain, specific diseases, and patients are most likely to incur harm from opioids.
3. Federal and non-federal agencies should sponsor the development and evaluation of multidisciplinary pain interventions, including cost-benefit analyses and identifying barriers to dissemination.

4. Federal and non-federal 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 for clinical settings.

5. 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 for analysis to better identify patients who respond to or have harm from opioid use.

6. Researchers on the effectiveness and harm of opioids should consider alternative designs (e.g., N of 1 trials, qualitative studies, implementation science, secondary analysis, Phase 1 and 2 design) in addition to randomized clinical trials.

7. Federal and non-federal agencies should sponsor research on risk identification and mitigation strategies prior to widespread integration of opioid use for chronic pain into clinical care.

8. Federal and non-federal 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.

9. 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.

10. NIH or other federal agencies should sponsor conferences to promote harmonization of guidelines of professional organizations to facilitate their implementation more consistently in clinical care.

Summary

The rise 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 where 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 and potentially harmful. Many roots of the problem stem from inadequate knowledge about the best approaches to treat various types of pain, balancing the effectiveness with the potential for harm, as well as a dysfunctional health care delivery system that promotes clinicians prescribing the easiest rather than the best approach to addressing pain. The EPC report identified few studies that were able to answer the key questions, suggesting the dire need for research on the effectiveness and safety of opioids as well as optimal management and risk mitigation strategies. What was particularly striking to the panel was the realization that there is insufficient evidence for every clinical decision that a provider needs to make regarding 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 design and analytic methods will be 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.

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