GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN

IMPROVING PRACTICE THROUGH RECOMMENDATIONS

CDC’s Guideline for Prescribing Opioids for Chronic Pain is intended to improve communication between providers and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder and overdose. The Guideline is not intended for patients who are in active cancer treatment, palliative care, or end-of-life care.

DETERMINING WHEN TO INITIATE OR CONTINUE OPIOIDS FOR CHRONIC PAIN

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.

2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.

3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

CLINICAL REMINDERS

- Opioids are not first-line or routine therapy for chronic pain
- Establish and measure goals for pain and function
- Discuss benefits and risks and availability of nonopioid therapies with patient
When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.

When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to $\geq 50$ morphine milligram equivalents (MME)/day, and should avoid increasing dosage to $\geq 90$ MME/day or carefully justify a decision to titrate dosage to $\geq 90$ MME/day.

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.

Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages ($\geq 50$ MME/day), or concurrent benzodiazepine use, are present.

Clinicians should review the patient’s history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.

When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.

Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.

Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.
The CDC Guideline on Opioid Prescribing
Rising to the Challenge

Yngvild Olsen, MD, MPH

In 2014, nearly 20,000 deaths due to overdose of prescription opioids occurred in the United States.1 That same year, more than 10 million people in the United States reported using prescription opioids for nonmedical reasons, and close to 2 million people older than 12 years met diagnostic criteria for a substance use disorder involving prescription opioids.2 This is the highest number of individuals considered to have opioid addiction since statistics began to be collected in the late 19th century.3 Four of 5 persons newly initiating heroin use now report starting with a prescription opioid, a near complete reversal since prior to 2000.4 Despite multiple, laudable efforts across the country aimed at curbing the opioid epidemic, there seems to be little relief in sight.

In the 1980s and 1990s, a body of evidence documented that patients commonly experience inadequately treated pain. Researchers found systemic health disparities in access to pain management.5 National authorities, including the Federation of State Medical Boards, called on health care practitioners to pay greater attention to pain.6 In 2000, the Joint Commission adopted pain as the “fifth vital sign,”7 a well-intentioned (albeit simplistic) policy to increase awareness of and interventions for pain.

These efforts to treat pain more effectively coincided with relentless and misleading marketing of prescription opioids by manufacturers, who minimized the risks of misuse and addiction.8 These efforts also coincided with the introduction of patient satisfaction surveys tied to physician performance and reimbursement in some areas, including the assessment of pain.

In retrospect, it is significant that this campaign occurred in the absence of substantial evidence for the long-term effectiveness of opioids in the treatment of persistent pain outside of active cancer and palliative care and without substantial training, understanding, and acknowledgment of addiction as a preventable, identifiable, and treatable disease.

Without strong evidence or sufficient training, clinicians had to rely on their best clinical judgment influenced by opinion, beliefs, values, and past experience. However, prescribers proved to be as vulnerable as patients to conflicting messages and judgmental attitudes. For chronic pain management with prescription opioids, the benefit-risk analysis over the past 2 decades became so distorted that it led some clinicians to either miss or dismiss the presence of addiction in their patients, avoid discussing the possibility of this diagnosis, or stereotype patients with addiction and discharge them from care.9,10

Once established, patterns of clinical care can be extraordinarily resistant to change. For instance, in 2012, US health care practitioners wrote more than 200 million prescriptions for opioids, double the number in 1998 and 10 million more than in 2008.11 In addition, some evidence suggests that some physicians keep prescribing opioids to patients who have experienced serious harms such as overdose.12 Furthermore, as illustrated in 2 research letters by Wunsch et al13 and Baker et al,14 respectively, in this issue of JAMA, patients are receiving more opioids than in the past for common surgical procedures15 and from practitioners such as dentists who previously may have recommended nonopioid medication for procedures such as dental extractions.14

Using a database of health encounters of 14 million commercially insured adult patients, Wunsch et al13 reported that 80% of 155,297 patients who underwent any of 4 low-risk surgical procedures (carpal tunnel release, laparoscopic cholecystectomy, inguinal hernia repair, knee arthroscopy) filled a prescription for any opioid. The percentage filling prescriptions increased for all 4 procedures during the study years. For example, 72.4% filled prescriptions after carpal tunnel release in 2004 compared with 76.1% in 2012.

Using a national database of deidentified Medicaid transactions from 2000 to 2010 for surgical dental extraction, Baker et al14 found that 42% of 2,757,273 patients filled a prescrip-
tion for an opioid medication within 7 days of extraction, with a median of 120 mg of morphine milligram equivalents (MME) dispensed per prescription (ie, representing 24 tablets of 5 mg of hydrocodone).

Multiple efforts to address clinical decision making for pain medications have failed to have a major effect. These include continuing medical education courses developed by the US Food and Drug Administration for long-acting opioids as part of a risk evaluation and mitigation strategy, specialty-led guidelines on safe opioid prescribing, action by some physician boards to require additional education about pain management, state-level prescription monitoring programs, and others.

Given the national concern about the epidemic of overdose from prescription medication, the Centers for Disease Control and Prevention (CDC) has responded with an opioid prescribing guideline. The agency is the first at the federal level to provide practical guidance to clinicians on the role of prescription opioids for chronic pain outside of active cancer or palliative care. The CDC's final recommendations are published in this issue of JAMA, along with contextual and evidentiary material. Simultaneously, the CDC's full guideline with supplementary information is being published in the Morbidity and Mortality Weekly Report.

The CDC’s efforts to develop these recommendations are an example of the aphorism “no good deed goes unpunished.” Critics attacked the agency for including individuals in early meetings who had expressed strong opinions about over-prescribing, for not taking pain considerations seriously enough, and for venturing into an area outside of its expertise. To its credit, CDC did not dismiss these concerns. The agency listened, undertaking a rigorous review and revision process that solicited input from as many stakeholders as possible over the last several months. The result is without question the most important guideline for primary care clinicians on prescribing opioids for chronic pain outside of active cancer and palliative care that exists today.

In the face of limited, low-quality evidence for the effectiveness of long-term chronic opioids, the CDC guidelines focus on practical ways primary care practitioners can minimize risks of overdose, misuse, and addiction from these medications. Many of the preventive recommendations will be familiar to clinicians from principles of good medication management: “Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.” (Recommendation 1)

Other recommendations may be less familiar to clinicians and are certainly not exclusive to primary care practitioners: “Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.” (Recommendation 11) “Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (> 50 MME/d), or concurrent benzodiazepine use, are present.” (Recommendation 8)

Widespread adoption of the CDC’s recommendations in clinical practice would help reverse the epidemic of opioid over-prescribing. However, as the CDC alludes to, success depends on simultaneously addressing significant gaps in the health care system.

Despite the availability of more continuing education courses on safe prescribing than ever, substantial deficiencies in physician education and training about addiction remain. These result in physicians routinely dismissing patients from a practice without providing or referring them to effective care to address misuse or addiction. Education about substance use disorders and chronic pain management should start in medical school and continue through residency training in all patient-care specialties. The CDC and other federal agencies should convene a summit with the Association of American Medical Colleges and the Accreditation Council for Graduate Medical Education with the goal of incorporating such training into core curricula requirements for medical education and postgraduate training. For prescribers already in practice, Congress should empower the Department of Health and Human Services and other agencies to develop mandatory training modules for all practitioners as a condition of prescriptive authority for opioids.

There are also enormous gaps in reimbursement, both for chronic pain and for addiction treatment. Insurers should reimburse for safe and effective nonpharmacological interventions for both of these conditions. Of critical importance is adequate coverage by Medicare, Medicaid, and private insurance for medication-assisted treatment for opioid addiction, including methadone and buprenorphine. There needs to be widespread recognition that these effective treatments are not substitution of one addiction for another but rather are medications that, like insulin for diabetes mellitus, allow patients to live productively, managing their disease. This requires changing language associated with addiction, undoing discriminatory policies affecting those taking methadone or buprenorphine, and countering negative attitudes toward people with addiction.

There is an innovation gap, with few available care models that give primary care practitioners the time, resources, and support to care for patients with complex chronic pain at risk for or with addiction. Supporting the development and evaluation of such models should be a top priority. In addition, as is often the case, more research is needed. Although research will not help in the short-term, it is needed to improve how
physicians prescribe opioids in the coming decades. Important questions to answer include how best to assess quality of pain medication prescribing, how to reduce stigma among physicians and patients, and how to effectively manage co-occurring chronic pain and addiction.

The CDC guideline for prescribing opioids for chronic pain is an important and essential step forward. With support from physicians across the country, as well as from policy makers at all levels, implementation of the recommendations in this guideline has the potential to improve and save many, many lives.

REFERENCES
Primary care clinicians find managing chronic pain challenging. Evidence of long-term efficacy of opioids for chronic pain is limited. Opioid use is associated with serious risks, including opioid use disorder and overdose.

**OBJECTIVE** To provide recommendations about opioid prescribing for primary care clinicians treating adult patients with chronic pain outside of active cancer treatment, palliative care, and end-of-life care.

**PROCESS** The Centers for Disease Control and Prevention (CDC) updated a 2014 systematic review on effectiveness and risks of opioids and conducted a supplemental review on benefits and harms, values and preferences, and costs. CDC used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to assess evidence type and determine the recommendation category.

**EVIDENCE SYNTHESIS** Evidence consisted of observational studies or randomized clinical trials with notable limitations, characterized as low quality using GRADE methodology. Meta-analysis was not attempted due to the limited number of studies, variability in study designs and clinical heterogeneity, and methodological shortcomings of studies. No study evaluated long-term (>1 year) benefit of opioids for chronic pain. Opioids were associated with increased risks, including opioid use disorder, overdose, and death, with dose-dependent effects.

**RECOMMENDATIONS** There are 12 recommendations. Of primary importance, nonopioid therapy is preferred for treatment of chronic pain. Opioids should be used only when benefits for pain and function are expected to outweigh risks. Before starting opioids, clinicians should establish treatment goals with patients and consider how opioids will be discontinued if benefits do not outweigh risks. When opioids are used, clinicians should prescribe the lowest effective dosage, carefully reassess benefits and risks when considering increasing dosage to 50 morphine milligram equivalents or more per day, and avoid concurrent opioids and benzodiazepines whenever possible. Clinicians should evaluate benefits and harms of continued opioid therapy with patients every 3 months or more frequently and review prescription drug monitoring program data, when available, for high-risk combinations or dosages. For patients with opioid use disorder, clinicians should offer or arrange evidence-based treatment, such as medication-assisted treatment with buprenorphine or methadone.

**CONCLUSIONS AND RELEVANCE** The guideline is intended to improve communication about benefits and risks of opioids for chronic pain, improve safety and effectiveness of pain treatment, and reduce risks associated with long-term opioid therapy.
The number of people experiencing chronic pain is substantial, with US prevalence estimated at 11.2% of the adult population. Patients should receive appropriate pain treatment based on a careful consideration of the benefits and risks of treatment options. Opioids are commonly prescribed for pain, with approximately 3% to 4% of the adult US population prescribed long-term opioid therapy. Evidence supports short-term efficacy of opioids in randomized clinical trials lasting primarily 12 weeks or less, and patients receiving opioid therapy for chronic pain report some pain relief when surveyed. However, few studies have been conducted to rigorously assess the long-term benefits of opioids for chronic pain (pain lasting >3 months) with outcomes examined at least 1 year later. Opioid pain medication use presents serious risks. From 1999 to 2014, more than 165,000 persons died of overdose related to opioid pain medication in the United States. In 2013 alone, an estimated 1.9 million persons abused or were dependent on prescription opioid pain medication. Primary care clinicians report concern about opioid pain medication misuse, find managing patients with chronic pain stressful, express concern about patient addiction, and report insufficient training in prescribing opioids.

The "CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016," is intended for primary care clinicians (eg, family physicians, internists, nurse practitioners, and physician assistants) who are treating patients with chronic pain (ie, pain conditions that typically last >3 months or past the time of normal tissue healing) in outpatient settings. The guideline is intended to apply to patients 18 years and older with chronic pain outside of active cancer treatment, palliative care, and end-of-life care. Some of the recommendations might be relevant for acute care settings or other specialists, such as emergency physicians or dentists, but use in these settings or by other specialists is not the focus of the guideline.

The guideline is intended to improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death. Clinical decision making should be based on a relationship between the clinician and patient and an understanding of the patient’s clinical situation, functioning, and life context. The recommendations in the guideline are voluntary, rather than prescriptive standards. They are based on emerging evidence, including observational studies or randomized clinical trials with notable limitations. Clinicians should consider the circumstances and unique needs of each patient when providing care. This Special Communication details evidence reviewed by and official recommendations issued by the Centers for Disease Control and Prevention (CDC) and provides key highlights from a more extensive guideline; the full guideline with detailed information on disclosures and conflict of interest protocols, methods, scientific findings, and recommendation rationales can be found in the Morbidity and Mortality Weekly Report (MMWR).

**Guideline Development Process**

**Grading of Recommendations Assessment, Development, and Evaluation Method**

CDC used the CDC Advisory Committee on Immunization Practices (ACIP) translation of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method for guideline development. Within the ACIP GRADE framework, the quality of a body of evidence was graded, and the recommendations were developed and placed into categories (A or B) based on the quality of evidence, balance of benefits and harms, values and preferences, and resource allocation (Box 1).

CDC obtained input from experts, stakeholders, the public, peer reviewers, and a federally chartered advisory committee in the development process. CDC drafted a set of recommendations and invited subject matter experts, primary care professional society representatives, and state agency representatives (Core Expert Group, listed at the end of the article) to provide individual perspectives on how CDC used the evidence to develop the recommendations. CDC asked experts to undergo a rigorous process to assess and manage possible conflicts of interest; full details on protocols and disclosures are reported in the MMWR. CDC also engaged partners from 10 federal agencies and a Stakeholder Review Group of 18 organizations (listed at the end of the article) to provide comment. CDC convened a constituent engagement webinar to obtain additional perspectives from constituents on the key recommendations. To obtain comments from the public on the full guideline, CDC published a notice in the Federal Register (80 FR 77351) announcing the availability of the guideline and the supporting clinical and contextual evidence reviews for public comment. Per the final information quality bulletin for peer review (https://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2005/m05-03.pdf), the guideline was peer reviewed because it provides influential scientific content, Development, and Evaluation (GRADE) method for guideline development. Within the ACIP GRADE framework, the quality of a body of evidence was graded, and the recommendations were developed and placed into categories (A or B) based on the quality of evidence, balance of benefits and harms, values and preferences, and resource allocation (Box 1).

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information. In addition, the National Center for Injury Prevention and Control Board of Scientific Counselors (BSC), a federal advisory committee, established an Opioid Guideline Workgroup (OGW) to review the guideline (members of the BSC and OGW are listed at the end of the article). The OGW issued a report of observations to the BSC. At an in-person meeting, the BSC considered the OGW report, deliberated on the draft guideline itself, and offered an additional opportunity for public comment. The BSC voted unanimously to support the observations made by the OGW; that CDC adopt the guideline recommendations that, according to the workgroup’s report, had unanimous or majority support; and that CDC further consider the guideline recommendations for which the group had mixed opinions. At each stage, CDC reviewed and carefully considered comments and revised the guideline.

Clinical Evidence Review
To inform the guideline development process, CDC updated a systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ) on the effectiveness and risks of long-term opioid treatment of chronic pain that addressed clinical questions about effectiveness of long-term opioid therapy for outcomes at least 1 year later related to pain, function, and quality of life. The effectiveness of short-term opioid therapy has been established previously. In randomized clinical trials 12 weeks or shorter in duration, opioids were moderately effective for pain relief, with small benefits for functional outcomes, although estimates varied, based on uncontrolled studies, a high percentage of patients discontinued long-term opioid use because of lack of efficacy and because of adverse events.3 Opioids have unique effects such as tolerance and physical dependence that might influence assessments of benefit over time. These effects raise questions about whether findings on short-term effectiveness of opioid therapy can be extrapolated to estimate benefits of long-term therapy for chronic pain. Thus, it is important to consider studies that provide data on long-term benefit. For opioid-related harms (overdose, fractures, falls, motor vehicle crashes), studies were included with outcomes measured at shorter intervals because such outcomes can occur early during opioid therapy.

The review also considered evidence related to initiation and titration, harms and adverse events, and risk mitigation. CDC updated the review with more recent studies. Because long-term opioid use may be affected by use of opioids for acute pain, CDC added a clinical question on the effects of prescribing opioids for acute pain on long-term use (Box 2).

CDC updated the systematic literature search using search terms for opioid therapy, specific opioids, chronic pain, and comparative study designs; assessed the overall strength of each body of evidence using methods developed by the GRADE Working Group; and qualitatively synthesized results. Complete methods and data for the clinical evidence review, including information about data sources and searches, study selection, data extraction and quality assessment, data synthesis, and update search yield and new evidence may be found in the MMWR and associated online appendices.11

The updated review revealed that evidence on long-term opioid therapy for chronic pain outside of end-of-life care remains limited, with insufficient evidence to determine long-term benefits, although evidence suggests risk of serious harms that is dose-dependent. Table 1 provides a summary of the evidence and the quality ratings assigned. Full details on methodology and findings are available in the 2014 AHRQ report7 and the MMWR report.11 The body of evidence for each clinical question was categorized as evidence type 3 or 4 (observational studies or randomized clinical trials with notable limitations or clinical experience and observation). We highlight important findings from the review for each key question (KQ) below.

KQ1: Effectiveness and Comparative Effectiveness
No study of opioid therapy vs placebo, no opioid therapy, or non-opioid therapy for chronic pain evaluated long-term (≥1 year) outcomes related to pain, function, or quality of life. Most placebo-controlled randomized clinical trials were 6 weeks or shorter in duration.7

KQ2: Harms and Adverse Events
Long-term opioid therapy was associated with problematic patterns of opioid use leading to clinically significant impairment or distress. Varying terminology has been used to reflect this pattern, including “addiction” (more informally), “opioid abuse and opioid dependence” (per Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition] [DSM-IV] or International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]), and “opioid use disorder” (per DSM-5). Such disorders are manifested by similar criteria, including unsuccessful efforts to reduce or control use and use resulting in social problems and a failure to fulfill major role obligations at work, school, or home. Disorders are different from tolerance (diminished response to a drug with repeated use) and physical dependence (adaptation to a drug that produces symptoms of withdrawal when the drug is stopped), both of which can exist without a diagnosed disorder.

Long-term opioid therapy was associated with an increased risk of an opioid abuse or dependence diagnosis (as defined by ICD-9-CM codes) vs no opioid prescription.33 In primary care settings, prevalence of opioid dependence (using DSM-IV criteria) ranged from 3% to 26%.15-17 Factors associated with increased risk of misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications.16,18 Opioid use was associated with a dose-dependent increased risk of fatal and non-fatally overdose19,20 (Table 2). Other risks associated with opioid use included cardiovascular events,28,29 endocrinologic harms,30,31 and road trauma.32

KQ3: Dosing Strategies
Initiation of therapy with an extended-release/long-acting (ER/LA) opioid was associated with greater risk of nonfatal overdose than initiation with an immediate-release opioid in 1 study, with risk greatest in the first 2 weeks after initiation of treatment.33 Three studies of various ER/LA opioids found no clear differences related to pain or function34-36; there were mixed findings regarding the differences between methadone and morphine in overall risk for nonfatal or fatal overdose.37-39 suggesting that risks of methadone might vary in different settings. One study found no differences between more liberal dose escalation and maintenance of current doses after 12 months39; evidence on other comparisons related to opioid dosing strategies was too limited to determine effects on outcomes.

KQ4: Risk Assessment and Risk Mitigation Strategies
Evidence on the accuracy of risk assessment instruments for predicting opioid abuse or misuse was inconsistent for the Opioid Risk

Box 2

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Box 2. Key Questions for the Clinical Evidence Review

### Key Question 1. Effectiveness and Comparative Effectiveness

- a. In patients with chronic pain, what is the effectiveness of long-term opioid therapy vs placebo or no opioid therapy for long-term (≥1 year) outcomes related to pain, function, and quality of life?
- b. How does effectiveness vary depending on: (1) the specific type or cause of pain (eg, neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); (2) patient demographics (eg, age, race, ethnicity, gender); and (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities, and high risk for addiction)?
- c. In patients with chronic pain, what is the comparative effectiveness of opioids vs nonopioid therapies (pharmacologic or nonpharmacologic) on outcomes related to pain, function, and quality of life?
- d. In patients with chronic pain, what is the comparative effectiveness of immediate-release plus nonopioid interventions (pharmacologic or nonpharmacologic) vs opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?

### Key Question 2. Harms and Adverse Events

- a. In patients with chronic pain, what are the risks of opioids vs placebo or no opioid on (1) opioid abuse, addiction, and related outcomes; (2) overdose, and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle crashes, endocrinologic harms, infections, cardiovascular events, cognitive harms, and psychological harms (eg, depression)?
- b. How do harms vary depending on (1) the specific type or cause of pain (eg, neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); (2) patient demographics; (3) patient comorbidities (including past or current substance use disorder or at high risk for addiction); and (4) the dose of opioids used?

### Key Question 3. Dosing Strategies

- a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- b. In patients with chronic pain, what is the comparative effectiveness of immediate-release vs extended-release/long-acting (ER/LA) opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- c. In patients with chronic pain, what is the comparative effectiveness of different ER/LA opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- d. In patients with chronic pain, what is the comparative effectiveness of immediate-release plus ER/LA opioids vs ER/LA opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?

### Key Question 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?
- 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?
- c. In patients with chronic pain prescribed long-term opioid therapy, what is the effectiveness of risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, and (8) use of abuse-deterrent formulations on outcomes related to overdose, addiction, abuse, or misuse?
- d. What is the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and quality of life?

### Key Question 5. Effect of Opioid Therapy for Acute Pain on Long-term Use

- a. In patients with acute pain, what are the effects of prescribing opioid therapy vs not prescribing opioid therapy for acute pain on long-term opioid use?

**KQ5: Effect of Opioid Therapy for Acute Pain on Long-term Use**

Studies examining patients who underwent low-risk surgery or experienced low back pain from injury revealed that opioid therapy prescribed for acute pain was associated with greater likelihood of long-term use.\(^{46,47}\) Compared with no early opioid use for acute low back pain, the adjusted odds ratio for receiving 5 or more opioid prescriptions from 30 to 730 days after onset was 2.08 (95% CI, 1.55-2.78) for 1 to 140 morphine milligram equivalents (MME) per day and increased to 6.14 (95% CI, 4.92-7.66) for 450 MME or more per day.\(^{47}\)
Table 1. GRADE Ratings of the Evidence for the Key Clinical Questions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Type of Evidence</th>
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<tbody>
<tr>
<td><strong>Effectiveness and Comparative Effectiveness (Key Question 1)</strong>&lt;br&gt;Effectiveness of long-term opioid therapy vs placebo or no opioid therapy for long-term (≥1 y) outcomes&lt;br&gt;Pain, function, and quality of life</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
<td>NA</td>
<td>No&lt;evidence.</td>
<td></td>
</tr>
<tr>
<td>Harms and Adverse Events (Key Question 2)&lt;br&gt;Risks of opioids vs placebo or no opioids on opioid abuse, addiction, and related outcomes; overdose; and other harms&lt;br&gt;Abuse or addiction</td>
<td>1 cohort study (n = 568,640)</td>
<td>Serious limitations</td>
<td>Unknown (1 study)</td>
<td>No imprecision</td>
<td>3</td>
<td>None identified</td>
<td>One retrospective cohort study found long-term use of prescribed opioids was associated with an increased risk of abuse or dependence diagnosis vs no opioid use (adjusted OR range, 1.49-12.25, depending on dose).</td>
</tr>
<tr>
<td>Abuse or addiction</td>
<td>10 uncontrolled studies (n = 3780)</td>
<td>Very serious limitations</td>
<td>Very serious inconsistency</td>
<td>No imprecision</td>
<td>4</td>
<td>None identified</td>
<td>In primary care settings, prevalence of opioid abuse ranged from 0.6%-8%; prevalence of dependence, 3%-26%. In pain clinic settings, prevalence of misuse, 8%-16%, and addiction, 2%-14%. Prevalence of aberrant drug-related behaviors, 6%-37%.</td>
</tr>
<tr>
<td>Overdose</td>
<td>1 cohort study (n = 9940)</td>
<td>Serious limitations</td>
<td>Unknown (1 study)</td>
<td>Serious imprecision</td>
<td>3</td>
<td>None identified</td>
<td>Current opioid use associated with increased risk of any overdose events, adjusted HR, 5.2 (95% CI, 2.1-12), and serious overdose events, adjusted HR, 8.4 (95% CI, 2.5-28) vs current nonuse.</td>
</tr>
<tr>
<td>Fractures</td>
<td>1 cohort study (n = 2,341) 1 case-control study (n = 21,739 case patients)</td>
<td>Serious limitations</td>
<td>No inconsistency</td>
<td>No imprecision</td>
<td>3</td>
<td>None identified</td>
<td>Opioid use associated with increased risk of fracture in 1 cohort study, adjusted HR, 1.28 (95% CI, 0.99-1.64), and 1 case-control study, adjusted OR, 1.27 (95% CI, 1.21-1.33).</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 cohort study (n = 426,124) 1 case-control study (n = 11,693 case patients)</td>
<td>No limitations</td>
<td>No inconsistency</td>
<td>No imprecision</td>
<td>3</td>
<td>None identified</td>
<td>Current opioid use associated with increased risk of myocardial infarction vs nonuse, adjusted OR, 1.28 (95% CI, 1.19-1.37) and IRR, 2.66 (95% CI, 2.30-3.08).</td>
</tr>
<tr>
<td>Endocrinologic harms</td>
<td>1 cross-sectional study (n = 11,327)</td>
<td>Serious limitations</td>
<td>Unknown (1 study)</td>
<td>No imprecision</td>
<td>3</td>
<td>None identified</td>
<td>Long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement vs nonuse, adjusted OR, 1.5 (95% CI, 1.1-1.9).</td>
</tr>
<tr>
<td>How do harms vary depending on the opioid dose used?&lt;br&gt;Abuse or addiction</td>
<td>1 cohort study (n = 568,640)</td>
<td>Serious limitations</td>
<td>Unknown (1 study)</td>
<td>No imprecision</td>
<td>3</td>
<td>None identified</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 with no opioid prescription, the adjusted ORs were 1.5 (95% CI, 1.0-2.1) for 1-36 MME/d, 2.9 (95% CI, 2.0-4.1) for 36-120 MME/d, and 12.2 (95% CI, 7.3-20.5) for ≥120 MME/d.</td>
</tr>
</tbody>
</table>

(continued)
### Table 1. GRADE Ratings of the Evidence for the Key Clinical Questions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Type of Evidence</th>
<th>Other Factors</th>
<th>Estimates of Effect or Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overdose</strong></td>
<td>1 cohort study (n = 9940) and 1 case-control study (n = 593 case patients in primary analysis)</td>
<td>Serious limitations</td>
<td>No inconsistency</td>
<td>No imprecision</td>
<td>3</td>
<td>Magnitude of effect, dose-response relationship</td>
<td>Compared with 1–20 MME/d, 1 cohort study found an adjusted HR for an overdose event of 1.44 (95% CI, 0.57-3.62) for 20–50 MME/d that increased to 8.87 (95% CI, 3.99-19.72) at &gt;100 MME/d; 1 case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI, 0.94-1.84) for 20–49 MME/d that increased to 2.88 (95% CI, 1.79-4.63) at ≥200 MME/d.</td>
</tr>
<tr>
<td>Fractures</td>
<td>1 cohort study (n = 2341)</td>
<td>Serious limitations</td>
<td>Unknown (1 study)</td>
<td>No imprecision</td>
<td>3</td>
<td>None identified</td>
<td>Risk of fracture increased from an adjusted HR of 1.20 (95% CI, 0.92-1.56) at 1–20 MME/d to 2.00 (95% CI, 1.24-3.24) at ≥50 MME/d; the trend was of borderline statistical significance.</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 cohort study (n = 426 124)</td>
<td>Serious limitations</td>
<td>Unknown (1 study)</td>
<td>No imprecision</td>
<td>3</td>
<td>None identified</td>
<td>Relative to a cumulative dose of 0–1350 MME during a 90-d period, the IRR for myocardial infarction for 1350–&lt;2700 MME was 1.21 (95% CI, 1.02-1.45); for 2700–&lt;8100 MME, 1.42 (95% CI, 1.21-1.67); for 8100–18 000 MME, 1.89 (95% CI, 1.54-2.33); and for ≥18 000 MME, 1.73 (95% CI, 1.32-2.26).</td>
</tr>
<tr>
<td>Motor vehicle crash injuries</td>
<td>1 case-control study (n = 5300 case patients)</td>
<td>No limitations</td>
<td>Unknown (1 study)</td>
<td>No imprecision</td>
<td>3</td>
<td>None identified</td>
<td>No association between opioid dose and risk of motor vehicle crash injuries even though opioid dosages ≥20 MME/d were associated with increased odds of road trauma among drivers.</td>
</tr>
<tr>
<td>Endocrinologic harms</td>
<td>1 cross-sectional study (n = 11 327); new for update: 1 additional cross-sectional study (n = 1585)</td>
<td>Serious limitations</td>
<td>Consistent</td>
<td>No imprecision</td>
<td>3</td>
<td>None identified</td>
<td>Relative to 0–20 MME/d, the adjusted OR for ≥120 MME/d for use of medications for erectile dysfunction or testosterone replacement was 1.6 (95% CI, 1.0-2.4). One new cross-sectional study found higher-dose long-term opioid therapy associated with increased risk of androgen deficiency among men receiving immediate-release opioids, adjusted OR per 10 MME/d, 1.16 (95% CI, 1.09-1.23), but the dose response was very weak among men receiving ER/LA opioids.</td>
</tr>
</tbody>
</table>

### Dosing Strategies (Key Question 3)

Comparative effectiveness of different methods for initiating opioid therapy and titrating doses

<table>
<thead>
<tr>
<th>Pain</th>
<th>3 randomized trials (n = 93)</th>
<th>Serious limitations</th>
<th>Serious inconsistency</th>
<th>Very serious imprecision</th>
<th>4</th>
<th>Trials on effects of titration with immediate-release vs ER/LA opioids reported inconsistent results and had additional differences between treatment groups in dosing protocols (titrated vs fixed dosing) and doses of opioids used.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overdose</td>
<td>New for update: 1 cohort study (n = 840 606)</td>
<td>Serious limitations</td>
<td>Unknown (1 study)</td>
<td>No imprecision</td>
<td>4</td>
<td>One new cross-sectional study found initiation of therapy with an ER/LA opioid associated with increased risk of overdose vs initiation with an immediate-release opioid, adjusted HR, 2.33 (95% CI, 1.64-3.32).</td>
</tr>
</tbody>
</table>
Table 1. GRADE Ratings of the Evidence for the Key Clinical Questionsa (continued)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Type of Evidenceb</th>
<th>Other Factors</th>
<th>Estimates of Effect or Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparative effectiveness of different ER/LA opioids</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pain and function</td>
<td>3 randomized trials (n = 1850)</td>
<td>Serious limitations</td>
<td>No inconsistency</td>
<td>No imprecision</td>
<td>3</td>
<td>None identified</td>
<td>No differences.</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1 cohort study (n = 108492); new for update: 1 cohort study (n = 38756)</td>
<td>Serious limitations</td>
<td>Serious inconsistency</td>
<td>No imprecision</td>
<td>4</td>
<td>None identified</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, adjusted HR, 0.56 (95% CI, 0.51-0.62). One cohort study among Tennessee Medicaid patients found methadone to be associated with higher risk of all-cause mortality than sustained-release morphine, adjusted HR, 1.46 (95% CI, 1.17-1.73).</td>
</tr>
<tr>
<td>Abuse and related outcomes</td>
<td>1 cohort study (n = 5684)</td>
<td>Serious limitations</td>
<td>Unknown (1 study)</td>
<td>Serious imprecision</td>
<td>4</td>
<td>None identified</td>
<td>One cohort study found some differences between ER/LA opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions.</td>
</tr>
<tr>
<td>ER/LA vs immediate-release opioids</td>
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</tr>
<tr>
<td>Endocrinologic harms</td>
<td>New for update: 1 cross-sectional study (n = 1585)</td>
<td>Serious limitations</td>
<td>Unknown (1 study)</td>
<td>No imprecision</td>
<td>4</td>
<td>None identified</td>
<td>One cross-sectional study found ER/LA opioids associated with increased risk of androgen deficiency vs immediate-release opioids, adjusted OR, 3.39 (95% CI, 2.39-4.77).</td>
</tr>
<tr>
<td>Dose escalation vs dose maintenance or use of dose thresholds</td>
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<tr>
<td>Pain, function, or withdrawal due to opioid misuse</td>
<td>1 randomized trial (n = 140)</td>
<td>Serious limitations</td>
<td>Unknown (1 study)</td>
<td>Very serious imprecision</td>
<td>3</td>
<td>None identified</td>
<td>No difference between more liberal dose escalation vs 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 MME/day at the end of the trial).</td>
</tr>
<tr>
<td>Immediate-release vs ER/LA opioids, immediate-release plus ER/LA opioids vs ER/LA opioids alone, scheduled and continuous vs as-needed dosing of opioids, or opioid rotation vs maintenance of current therapy</td>
<td></td>
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</tr>
<tr>
<td>Pain, function, quality of life, and outcomes related to abuse</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
<td>NA</td>
<td>No evidence.</td>
</tr>
<tr>
<td>Effects of decreasing or tapering opioid doses vs continuation of opioid therapy</td>
<td></td>
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</tr>
<tr>
<td>Pain and function</td>
<td>1 randomized trial (n = 10)</td>
<td>Very serious limitations</td>
<td>Unknown (1 study)</td>
<td>Very serious imprecision</td>
<td>4</td>
<td>None identified</td>
<td>Abrupt cessation of morphine was associated with increased pain and decreased function compared with continuation of morphine.</td>
</tr>
<tr>
<td>Comparative effectiveness of different tapering protocols and strategies</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Opioid abstinence</td>
<td>2 nonrandomized trials (n = 150)</td>
<td>Very serious limitations</td>
<td>No inconsistency</td>
<td>Very serious imprecision</td>
<td>4</td>
<td>None identified</td>
<td>No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3-6 mo.</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Type of Evidence</th>
<th>Other Factors</th>
<th>Estimates of Effect or Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Assessment and Risk Mitigation Strategies (Key Question 4)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Diagnostic accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse among patients with chronic pain being considered for long-term opioid therapy</td>
<td></td>
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</tr>
<tr>
<td>Opioid Risk Tool</td>
<td>3 studies of diagnostic accuracy (n = 496); new for update: 2 studies of diagnostic accuracy (n = 320)</td>
<td>Serious limitations</td>
<td>Very serious inconsistency</td>
<td>Serious imprecision</td>
<td>4</td>
<td>None identified</td>
<td>Based on a cutoff score of &gt;4 (or unspecified), 5 studies (2 fair-quality, 3 poor-quality) reported sensitivity that ranged from 0.20-0.99 and specificity that ranged from 0.16-0.88.</td>
</tr>
<tr>
<td>Screener and opioid assessment for patients with pain, version 1</td>
<td>2 studies of diagnostic accuracy (n = 203)</td>
<td>Very serious limitations</td>
<td>No inconsistency</td>
<td>Serious imprecision</td>
<td>3</td>
<td>None identified</td>
<td>Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity was 0.38 in 1 study, for a positive likelihood ratio of 1.11 and a negative likelihood ratio of 0.83. Based on a cutoff score of &gt;6, sensitivity was 0.73 in 1 study.</td>
</tr>
<tr>
<td>Screener and opioid assessment for patients with pain: revised</td>
<td>New for update: 2 studies of diagnostic accuracy (n = 320)</td>
<td>Very serious limitations</td>
<td>No inconsistency</td>
<td>Serious imprecision</td>
<td>3</td>
<td>None identified</td>
<td>Based on a cutoff score of &gt;3 or unspecified, sensitivity was 0.25 and 0.53 and specificity was 0.62 and 0.73 in 2 studies, for likelihood ratios close to 1.</td>
</tr>
<tr>
<td>Brief risk interview</td>
<td>New for update: 2 studies of diagnostic accuracy (n = 320)</td>
<td>Very serious limitations</td>
<td>No inconsistency</td>
<td>Serious imprecision</td>
<td>3</td>
<td>None identified</td>
<td>Based on a “high-risk” assessment, sensitivity was 0.73 and 0.83 and specificity was 0.43 and 0.88 in 2 studies, for positive likelihood ratios of 1.28 and 7.18 and negative likelihood ratios of 0.63 and 0.19.</td>
</tr>
<tr>
<td>Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes related to abuse</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
<td>NA</td>
<td>No evidence.</td>
</tr>
<tr>
<td>Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes related to abuse</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
<td>NA</td>
<td>No evidence.</td>
</tr>
<tr>
<td>Comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes related to abuse</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
<td>NA</td>
<td>No evidence.</td>
</tr>
</tbody>
</table>
Contextual Evidence Review

CDC conducted a contextual evidence review to assist in developing the recommendations by providing an assessment of the balance of benefits and harms, values and preferences, and cost, consistent with the GRADE approach (Box 3). Rapid review methods were used to streamline the process and obtain evidence quickly (eg, by limiting database searches and summarizing study quality based on author reports rather than applying objective quality rating protocols). Full details on methodology, including data sources and searches, inclusion criteria, study selection, and data extraction and synthesis, and findings are available in the MMWR report.11 In this article, we summarize benefits and harms of nonopioid therapies found in the clinical literature and harms of opioid therapy, including additional studies not included in the clinical evidence review (eg, studies not restricted to patients with chronic pain).

Several nonpharmacologic and nonopioid pharmacologic treatments were found to be effective for chronic pain in studies ranging in duration from 2 weeks to 6 months48-66 (Table 3). For example, cognitive behavioral therapy (CBT) had small positive effects on disability and catastrophic thinking.66 Exercise therapy reduced pain and improved function in chronic low back pain54; improved function and reduced pain in osteoarthritis of the knee53 and hip52; and improved well-being, fibromyalgia symptoms, and physical function in fibromyalgia.48 Multimodal and multidisciplinary therapies helped reduce pain and improve function more effectively than single modalities.55,67 Multiple guidelines recommended acetaminophen as first-line pharmacotherapy for osteoarthritis68-73 or for low back pain74 and nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line treatment for osteoarthritis or low back pain70,74; first- and second-line drugs for neuropathic pain include anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors (SNRIs).75-78 Nonsteroidal anti-inflammatory drugs have been associated with hepatic, gastrointestinal, renal, and cardiovascular risks.63,73,79

Opioid-related overdose risk was dose-dependent, with higher opioid dosages associated with increased overdose risk (Table 2).19-27 Compared with dosages of 1 to <20 MME per day, dosages of 50 to <100 MME per day were found to increase risks for opioid overdose by factors of 1.920 to 4.6,22 with absolute risk difference approximation of 0.15% for fatal overdose22 and 1.40% for any overdose;19 dosages of 100 MME or more per day were found to increase risks for opioid overdose by factors of 2.020 to 8.919 relative to dosages of 1 to <20 MME per day, with absolute risk difference approximation 0.25% for fatal overdose22 and 4.04% for any overdose.19 Veterans Health Administration patients with chronic pain who died of overdoses related to opioids were prescribed higher mean opioid dosages (98 MME/d) than controls (48 MME/d)27, above 200 MME per day, mortality rates continue to increase more gradually.23 (See Table 4 and Box 4 for a list of common opioid medications and their MME equivalents.)

Other findings included disproportionate numbers of overdose deaths associated with methadone80; fatal overdose risk associated with co-prescription of opioids and benzodiazepines80,23,81 and risks associated with sleep-disordered breathing,82,83 reduced renal or hepatic function,84 older age,85-88 pregnancy,89-92 mental health comorbidities, and history of substance use disorder.86,93,94 Indirect evidence was found for potential utility of
risk stratification and mitigation strategies for identifying risky opioid-taking behaviors and prescribing practices, such as checking prescription drug monitoring program (PDMP) data and urine drug testing, as well as co-prescription of naloxone. In addition, methadone and buprenorphine for opioid use disorder were found to increase retention in treatment and to decrease illicit opioid use among patients with opioid use disorder, and some studies suggest that effectiveness is enhanced when psychosocial treatments are used in conjunction with medication-assisted therapy.

### Recommendations

The guideline includes 12 recommendations (Box 5). GRADE recommendation categories were based on the following assessment:

- No evidence shows a long-term benefit of opioids in pain and function vs no opioids for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized clinical trials ≤6 weeks in duration).
- Extensive evidence shows the possible harms of opioids (including opioid use disorder, overdose, and motor vehicle injury).
- Extensive evidence suggests some benefits of nonpharmacologic and nonopioid pharmacologic therapy, with less harm.

### Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy.

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**Table 2. Relationship Between Dose and Overdose**

<table>
<thead>
<tr>
<th>Source</th>
<th>Topic</th>
<th>Population</th>
<th>Primary Outcomes</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bohnert et al., 2016</td>
<td>Matched case-control study examining association between opioid dosage and fatal overdose</td>
<td>Veterans Health Administration patients with chronic pain receiving opioid therapy, 2004-2009</td>
<td>Unintentional fatal opioid overdose</td>
<td>24% of controls had dosages &gt;50 MME/d, but 55% of cases had dosages above this level.</td>
</tr>
<tr>
<td>Bohnert et al., 2011</td>
<td>Case-cohort study examining the association between prescribed opioid dosage in MME/d and risk of opioid overdose death</td>
<td>Veterans Health Administration patients receiving opioid therapy for pain, 2004-2005</td>
<td>Fatal opioid overdose</td>
<td>Among patients with chronic pain, receiving 20-&lt;50 MME/d, 50-&lt;100 MME/d, and ≥100 MME/d was associated with adjusted HRs for overdose death of 1.88, 4.63, and 7.18 compared with 1-&lt;20 MME/d.</td>
</tr>
<tr>
<td>Dasgupta et al., 2015</td>
<td>Prospective observational cohort study investigating fatal overdose among patients receiving opioid pain medication</td>
<td>Residents of North Carolina receiving a prescription for opioid pain medication</td>
<td>Overdose death involving opioid pain medication</td>
<td>Overdose risk increased steadily in a dose-dependent manner; rate of increase decreased after 200 MME/d. Evidence of concurrent benzodiazepine prescription in the past year was 80%, and benzodiazepines were determined to be involved in 61% of deaths involving opioid pain medications.</td>
</tr>
<tr>
<td>Dunn et al., 2010</td>
<td>Cohort study examining rates of opioid overdose and association with opioid dosage among patients receiving chronic opioid therapy</td>
<td>Health maintenance organization patients who received ≥3 opioid prescriptions within 90 d for chronic noncancer pain</td>
<td>Opioid-related overdose (fatal or nonfatal)</td>
<td>Compared with receiving 1-&lt;20 MME/d, receiving 20-&lt;50 MME/d, 50-&lt;100 MME d, and &gt;100 MME/d was associated with adjusted HRs for overdose of 1.4, 3.7, and 8.9.</td>
</tr>
<tr>
<td>Gomes et al., 2011</td>
<td>Case-control study examining association between opioid dose level and opioid-related mortality</td>
<td>Ontario residents aged 15-64 y who received an opioid for nonmalignant pain through public prescription drug coverage, 1997-2006</td>
<td>Coroner’s determination of opioid-related death</td>
<td>Compared with receiving 1-&lt;20 MME/d, receiving 20-49 MME/d, 50-99 MME d, and 100-199 MME/d was associated with odds ratios for fatal overdose of 1.3, 1.9, and 2.0.</td>
</tr>
<tr>
<td>Gwira et al., 2014</td>
<td>Matched case-control study examining association between opioid dosage level and opioid-related mortality</td>
<td>Patients enrolled in Tennessee Controlled Substances Monitoring Program, 2007-2011</td>
<td>Fatal overdose</td>
<td>Opioid-related overdose death was associated with &gt;100 MME/d, ≥4 prescribers, and ≥4 pharmacies (adjusted odds ratios, 1.2, 6.5, and 6.0). At least one of these risk factors was present in 55% of overdose deaths.</td>
</tr>
<tr>
<td>Liang and Turner, 2015</td>
<td>Longitudinal cohort study examining association between opioid dosage levels and overdose</td>
<td>Health maintenance program enrollees who filled at least 2 schedule II or III opioid analgesics prescriptions from January 2009 through July 2012</td>
<td>Fatal overdose</td>
<td>Overdose risk was associated with daily opioid dosage. In addition, among patients prescribed 50-100 MME/d, overdose risk was significantly greater for patients prescribed &gt;1830 MME cumulatively over 6 mo.</td>
</tr>
<tr>
<td>Pauluzzi et al., 2012</td>
<td>Matched case-control study examining overdose death and patterns of use of opioid analgesics</td>
<td>New Mexico residents who died of unintentional drug overdoses and patients with prescriptions in the Prescription Monitoring Program, April 2006-March 2008</td>
<td>Fatal overdose</td>
<td>Patients receiving a daily average dose of &gt;40 MME had a 12.2 greater odds of overdose compared with those with lower opioid dosages or no opioid prescriptions.</td>
</tr>
<tr>
<td>Zedler et al., 2014</td>
<td>Association between opioid dose and overdose</td>
<td>Patients dispensed an opioid by the Veterans Health Administration, 2010-2012</td>
<td>Respiratory/central nervous system depression, overdose</td>
<td>Compared with patients with 1-&lt;20 MME/d, the odds ratio of overdose was 1.5 for patients prescribed 20-&lt;50 MME/d, 2.2 for patients prescribed 50-&lt;100 MME/d, and 4.3 for patients prescribed ≥100 MME/d.</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; MME, morphine milligram equivalents.

* Included in the contextual evidence review.

* Included in the clinical evidence review.
Box 3. Key Areas for the Contextual Evidence Review

- **Effectiveness of alternative treatments**, including nonpharmacologic (eg, cognitive behavioral therapy, exercise therapy, interventional treatments, multimodal pain treatment) and nonopioid pharmacologic treatments (eg, acetaminophen, nonsteroidal anti-inflammatory drugs, antidepressants, anticonvulsants), including studies of any duration.
- **Benefits and harms of opioid therapy** (including additional studies not included in the clinical evidence review, such as studies that were not restricted to patients with chronic pain, evaluated outcomes at any duration, performed ecological analyses, or used observational study designs other than cohort and case-cohort control studies) related to specific opioids, high-dose therapy, co-prescription with other controlled substances, duration of use, special populations, and potential usefulness of risk stratification or mitigation approaches; in addition to effectiveness of treatments associated with addressing potential harms of opioid therapy (opioid use disorder).
- **Clinician and patient values and preferences** related to opioids and medication risks, benefits, and use.
- **Resource allocation**, including costs and economic efficiency of opioid therapy and risk mitigation strategies.
- **Clinical guidelines** relevant to opioid prescribing to complement the Centers for Disease Control and Prevention recommendations (eg, guidelines on alternative treatments, guidelines with recommendations related to specific clinician actions such as urine drug testing or opioid tapering protocols).

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**2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and consider how opioid therapy will be discontinued if benefits do not outweigh risks.** Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety. (Recommendation category: A; evidence type: 4)

Before opioid therapy is initiated for chronic pain, clinicians should determine how effectiveness will be evaluated and should establish treatment goals with patients. Clinicians seeing new patients already receiving opioids should establish treatment goals for continued treatment. Goals should include improvement in both pain relief and function. However, there are some clinical circumstances under which reductions in pain without improvement in physical function might be a more realistic goal (eg, diseases typically associated with progressive functional impairment or catastrophic injuries such as spinal cord trauma). Experts noted that function can include emotional and social as well as physical dimensions. In addition, experts emphasized that mood has important interactions with pain and function. Clinicians may use validated instruments such as the 3-item “Pain average, interference with Enjoyment of life, and interference with General activity” (PEG) Assessment Scale to track patient outcomes. Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function. Because depression, anxiety, and other psychological comorbidities often coexist with and can interfere with resolution of pain, clinicians should use validated instruments to assess for these conditions and ensure that treatment for these conditions is optimized.

**3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.** (Recommendation category: A; evidence type: 3)

Clinicians should ensure that patients are aware of potential benefits of, harms of, and alternatives to opioids before starting or continuing opioid therapy. Clinicians are encouraged to have open and honest discussions with patients to inform mutual decisions about whether to start or continue opioid therapy. Important considerations include the following:

- Be explicit and realistic about expected benefits of opioids, explaining that while opioids can reduce pain during short-term use, there is no good evidence that opioids improve pain or function with long-term use and that complete relief of pain is unlikely.
- Emphasize improvement in function as a primary goal and that function can improve even when pain is still present.
- Advise patients about serious adverse effects of opioids, including potentially fatal respiratory depression and development of a potentially serious lifelong opioid use disorder.
- Advise patients about common effects of opioids, such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opioids.
- Discuss effects that opioids may have on ability to safely operate a vehicle, particularly when opioids are initiated, when dosages are increased, or when other central nervous system depressants, such as benzodiazepines or alcohol, are used concurrently.
### Table 3. Effectiveness and Harms of Nonpharmacologic and Nonopioid Pharmacologic Treatments

<table>
<thead>
<tr>
<th>Source</th>
<th>Topic or Intervention</th>
<th>Participants or Population</th>
<th>Primary Outcomes</th>
<th>Key Findings</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busch et al, 2007</td>
<td>Exercise training vs untreated control or nonexercise intervention</td>
<td>Systematic review of 33 RCTs with fibromyalgia patients</td>
<td>Global well-being, selected signs and symptoms, and physical function</td>
<td>Exercise training improves global well-being and physical function. Supervised aerobic exercise training has beneficial effects on physical capacity and fibromyalgia symptoms.</td>
<td>Four studies were classified as high quality, 15 as moderate quality, and 14 as low quality</td>
</tr>
<tr>
<td>Chaparro et al, 2014</td>
<td>Noninjectable opioids vs placebo or other treatments</td>
<td>Systematic review of 15 RCTs with patients with chronic low back pain</td>
<td>Pain</td>
<td>One trial found tramadol similar to celecoxib for pain relief. Two trials did not find a difference between opioids and antidepressants for pain or function.</td>
<td>Low-to moderate-quality evidence</td>
</tr>
<tr>
<td>Collins et al, 2000</td>
<td>Antidepressants vs placebo; anticonvulsants vs placebo</td>
<td>Systematic review of 19 RCTs for diabetic neuropathy or postherpetic neuralgia</td>
<td>Pain</td>
<td>For diabetic neuropathy, the NNT for ≥50% pain relief was 3.4 for antidepressants (12 trials, 10 evaluated TCAs and 3 SSRIs) and 2.7 for anticonvulsants (3 trials). For postherpetic neuralgia, the NNT was 2.1 for antidepressants (3 studies evaluating TCAs) and 3.2 for anticonvulsants (1 study evaluating gabapentin).</td>
<td>The mean and median quality score for included studies was 4 on a scale of 1-5</td>
</tr>
<tr>
<td>Fransen et al, 2015</td>
<td>Exercise vs nonexercise group (active or no treatment)</td>
<td>Systematic review of 54 RCTs or quasi-randomized trials for knee osteoarthritis</td>
<td>Reduced joint pain or improved physical function and quality of life</td>
<td>Exercise reduced pain, improved function, and improved quality of life immediately after treatment; in studies providing posttreatment follow-up data, improved pain and function were sustained for 2-6 mo.</td>
<td>High-quality evidence for reduced pain and improved quality of life and moderate-quality evidence for improved function</td>
</tr>
<tr>
<td>Fransen et al, 2014</td>
<td>Exercise vs nonexercise group (active or no treatment)</td>
<td>Systematic review of 10 RCTs or quasi-randomized trials for hip osteoarthritis</td>
<td>Reduced joint pain and improved physical function and quality of life</td>
<td>Exercise reduced pain and improved function immediately after treatment; in studies providing posttreatment follow-up data, improved pain and function were sustained for at least 3-6 mo.</td>
<td>High-quality evidence for reduced pain and improved function</td>
</tr>
<tr>
<td>Häuser et al, 2013</td>
<td>Duloxetine vs placebo; milnacipran vs placebo</td>
<td>Systematic review of 10 RCTs for fibromyalgia patients</td>
<td>Benefits and harms</td>
<td>Duloxetine and milnacipran reduced pain by a small amount compared with placebo.</td>
<td>Risk of bias in included studies was low</td>
</tr>
<tr>
<td>Hayden et al, 2005</td>
<td>Exercise therapy vs no treatment, other conservative treatments</td>
<td>Systematic review consisting of 61 RCTs for low back pain</td>
<td>Pain, function</td>
<td>Exercise therapy reduces pain and improves function with small magnitudes of effect. Effectiveness of exercise therapy appears to be greater in populations visiting a health care provider compared with the general population.</td>
<td>Only a small number of studies rated as high quality; potential publication bias</td>
</tr>
<tr>
<td>Lee et al, 2014</td>
<td>CIM therapies vs single self-care CIM, non-self-care CIM, usual care/no treatment, other multimodal program, or other control</td>
<td>Systematic review of 26 RCTs for management of chronic pain</td>
<td>Pain symptoms</td>
<td>Integrative multimodal therapies resulted in positive, but sometimes mixed, effects on pain symptoms compared with active controls or single self-care modalities. More studies are needed to make strong conclusions about effectiveness.</td>
<td>Large majority of poor quality, including weaknesses in randomization and allocation concealment</td>
</tr>
<tr>
<td>Lunn et al, 2014</td>
<td>Duloxetine vs placebo or other controls</td>
<td>Systematic review of 18 RCTs for neuropathic pain, chronic pain conditions without identified cause, or fibromyalgia</td>
<td>Benefits and harms of duloxetine</td>
<td>Duloxetine at 60 mg and 120 mg daily, but not lower dosages, were effective in reducing pain in diabetic peripheral neuropathy and in fibromyalgia.</td>
<td>Moderate-quality evidence for diabetic neuropathy; lower-quality evidence for fibromyalgia; some risk of bias</td>
</tr>
<tr>
<td>Moore et al, 2009</td>
<td>Pregabalin vs placebo or any active control</td>
<td>Systematic review of 25 double-blind RCTs for postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain, or fibromyalgia</td>
<td>Analgesic efficacy and associated adverse events</td>
<td>Pregabalin was effective in patients with postherpetic neuralgia, diabetic neuropathy, central neuropathic pain, and fibromyalgia at doses of 300 mg, 450 mg, and 600 mg (but not at 150 mg) daily. NNTs were generally ≤6 for moderate benefit in postherpetic neuralgia and diabetic neuropathy but ≥7 for fibromyalgia.</td>
<td>Studies all had Oxford quality scores based on randomization, blinding, and reporting of dropout ≥3 (out of maximum of 5)</td>
</tr>
<tr>
<td>Moore et al, 2014</td>
<td>Gabapentin vs placebo</td>
<td>Systematic review of 37 RCTs for neuropathic pain or fibromyalgia</td>
<td>Analgesic efficacy and adverse effects</td>
<td>Gabapentin was significantly more effective than placebo in reducing pain in diabetic neuropathy and postherpetic neuralgia. Evidence was insufficient for other conditions.</td>
<td>“Second-tier” evidence (some risk of bias, but adequate numbers in the trials)</td>
</tr>
</tbody>
</table>

(continued)
Table 3. Effectiveness and Harms of Nonpharmacologic and Nonopioid Pharmacologic Treatments* (continued)

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Roelofs et al., 2008</td>
<td>NSAIDs and COX-2 inhibitors vs control</td>
<td>Systematic review of 65 RCTs for nonspecific low back pain</td>
<td>Acute low back pain</td>
<td>NSAIDs are more effective than placebo for acute and chronic low back pain without sciatica, but have more adverse effects. NSAIDs are not more effective than acetaminophen but had more adverse effects. No type of NSAIDs, including COX-2 inhibitors, was found to be more effective than other NSAIDs.</td>
<td>Mixed high- and low-quality studies</td>
</tr>
<tr>
<td>Saarto et al., 2010</td>
<td>Antidepressants vs placebo or other controls</td>
<td>Systematic review of 61 RCTs for neuropathic pain</td>
<td>Pain</td>
<td>TCAs and venlafaxine have low NNTs (3.6 and 3.1, respectively) for at least moderate pain relief.</td>
<td>Study quality limited by insufficient reporting detail</td>
</tr>
<tr>
<td>Salerno et al., 2002</td>
<td>Antidepressants vs placebo</td>
<td>Systematic review of 9 RCTs for chronic back pain</td>
<td>Back pain</td>
<td>Antidepressants were associated with small but significant improvement in pain severity; improvements in function were not significant. Most (6) studies evaluated TCAs.</td>
<td>Moderate-quality studies</td>
</tr>
<tr>
<td>Staiger et al., 2003</td>
<td>Antidepressants vs placebo</td>
<td>Systematic review of 7 RCTs in patients with chronic low back pain</td>
<td>Back pain</td>
<td>Four of 5 studies evaluating TCA and tetracyclic antidepressants found significant improvement in chronic low back pain. Other antidepressants studied (2 studies evaluating SSRIs and 1 evaluating trazodone) did not show significant pain improvement.</td>
<td>Mixed quality (quality scores ranged from 11-19 out of 22)</td>
</tr>
<tr>
<td>Trelle et al., 2011</td>
<td>NSAIDs vs other NSAIDs or placebo</td>
<td>Meta-analysis of 31 RCTs comparing any NSAID with other NSAID or placebo for any medical condition</td>
<td>Myocardial infarction, stroke, cardiovascular death, death from any cause</td>
<td>Compared with placebo, NSAIDs were associated with increased risk of myocardial infarction, stroke, and cardiovascular death.</td>
<td>Generally high</td>
</tr>
<tr>
<td>Welsch et al., 2015</td>
<td>Opioids (including tramadol) vs nonopioids (including acetaminophen, NSAIDs/COX-2 inhibitors, mexiletine, anticonvulsants, antidepressants, and muscle relaxants)</td>
<td>Systematic review of 10 RCTs in patients with neuropathic pain, low back pain, or osteoarthritis</td>
<td>Efficacy (including various pain measures), tolerability, and safety</td>
<td>There was no significant difference between opioids and nonopioid analgesics in pain reduction; nonopioids were superior to opioids in improving physical function and were better tolerated. When patients from tramadol trials (n randomized = 2788) were removed from results of the review, results for pain and function for patients receiving opioids (morphine) compared with alternative drugs (n randomized = 223) had wide, overlapping confidence intervals. Improved tolerability for alternative drugs vs morphine remained significant.</td>
<td>One study had a high, 2 studies a moderate, and 7 studies a low study quality</td>
</tr>
<tr>
<td>Wiffen et al., 2014</td>
<td>Carbamazepine vs placebo or other active control</td>
<td>Systematic review consisting of 10 RCTs in adults with chronic neuropathic pain or fibromyalgia</td>
<td>Pain relief</td>
<td>Carbamazepine provided better pain relief than placebo for trigeminal neuralgia, diabetic neuropathy, and poststroke pain for ≥4 weeks. Dizziness and drowsiness were commonly reported with carbamazepine. In 4 studies, 65% of patients receiving carbamazepine vs 27% receiving placebo experienced ≥1 adverse event. In 8 studies, 3% of patients receiving carbamazepine withdrew because of adverse events (vs 0% taking placebo).</td>
<td>Third-tier evidence (trials involving small numbers of participants, considered likely to be biased, with outcomes of limited clinical utility, or both)</td>
</tr>
<tr>
<td>Williams et al., 2012</td>
<td>Cognitive behavioral therapy or behavioral therapy</td>
<td>Systematic review of 42 RCTs for patients with nonmalignant chronic pain except headache</td>
<td>Pain, disability, mood, and catastrophic thinking</td>
<td>Cognitive behavioral therapy was found to have small to moderate effects on pain, disability, mood, and catastrophic thinking immediately after treatment when compared with usual treatment or deferred cognitive behavioral therapy, but only effects on mood persisted at follow-up. Behavioral therapy had a positive effect on mood immediately after treatment.</td>
<td>Mean quality of study design, 15.8 out of 26 (SD 4.3; range, 9-24 out of 26)</td>
</tr>
</tbody>
</table>

Abbreviations: CIM, complementary and integrative multimodal; COX-2, cyclooxygenase 2; NNT, number needed to treat; NSAID, nonsteroidal anti-inflammatory drug; RCTs, randomized clinical trials; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

* All the studies in this table were included in the contextual evidence review.
• Discuss increased risks for opioid use disorder, respiratory depression, and death at higher dosages, along with the importance of taking only the amount of opioids prescribed.
• Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, illicit drugs such as heroin, or other opioids.
• Discuss risks to household members and other individuals if opioids are intentionally or unintentionally shared with others for whom they are not prescribed, including the possibility that others might experience overdose at the same or at lower dosage than prescribed for the patient and that young children are susceptible to unintentional ingestion. Discuss storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids.105
• Discuss the importance of periodic reassessment to ensure opioids are helping to meet patient goals and to allow opportunities for opioid discontinuation and consideration of additional non-pharmacologic and nonopioid pharmacologic treatment options if opioids are not effective or are harmful.
• Discuss planned use of precautions to reduce risks, including use of PDMP information and urine drug testing. Consider including discussion of naloxone use for overdose reversal.
• Consider whether cognitive limitations might interfere with management of opioid therapy (for older adults in particular), and if so, determine whether a caregiver can responsibly co-manage medication therapy. Discuss the importance of reassessing safer medication use with both the patient and caregiver.

### Opioid Selection, Dosage, Duration, Follow-up, and Discontinuation

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids. (Recommendation category: A; evidence type: 4)

Clinicians should not initiate opioid treatment with ER/LA opioids and should not prescribe ER/LA opioids for intermittent use. In general, avoiding the use of immediate-release opioids in combination with ER/LA opioids is preferable.

When an ER/LA opioid is prescribed, using a product with predictable pharmacokinetics and pharmacodynamics is preferred to minimize unintentional overdose risk.

• Methadone should not be the first choice for an ER/LA opioid. Only clinicians who are familiar with methadone’s unique risk profile and who are prepared to educate and closely monitor their patients—including risk assessment for QT prolongation and consideration of electrocardiographic monitoring—should consider prescribing methadone for pain.

• Because dosing effects of transdermal fentanyl are often misunderstood by both clinicians and patients, only clinicians who are familiar with the dosing and absorption properties of transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.

5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to 50 morphine milligram equivalents (MME) or more per day, and should avoid increasing dosage to 90 MME or more per day or carefully justify a decision to titrate dosage to 90 MME or more per day. (Recommendation category: A; evidence type: 3)

Clinicians should start opioids at the lowest effective dosage, use caution when increasing opioid dosages, and increase dosage by the smallest practical amount. Before increasing total opioid dosage to 50 MME or more per day, clinicians should reassess whether...
Box 5. Centers for Disease Control and Prevention Recommendations for Prescribing Opioids for Chronic Pain Outside of Active Cancer, Palliative, and End-of-Life Care

Determining When to Initiate or Continue Opioids for Chronic Pain
1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.

2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.

3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

Opioid Selection, Dosage, Duration, Follow-up, and Discontinuation
4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.

5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to 50 morphine milligram equivalents (MME) or more per day, and should avoid increasing dosage to 90 MME or more per day or carefully justify a decision to titrate dosage to 90 MME or more per day.

6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed.

7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

Assessing Risk and Addressing Harms of Opioid Use
8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/d), or concurrent benzodiazepine use are present.

9. Clinicians should review the patient’s history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.

10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.

11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.

12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

All recommendations are category A (apply to all patients outside of active cancer treatment, palliative care, and end-of-life care) except recommendation 10 (designated category B, with individual decision making required), detailed ratings of the evidence supporting the recommendations are provided in the full guideline publication.11

opioids are meeting the patient’s treatment goals. If a patient’s opioid dosage for all sources of opioids combined reaches or exceeds 50 MME per day, clinicians should implement additional precautions, including increased frequency of follow-up and considering offering naloxone. Clinicians should avoid increasing opioid dosages to 90 MME or more per day or should carefully justify a decision to increase dosage to 90 MME or more per day based on individualized assessment of benefits and risks and weighing factors such as diagnosis, incremental benefits for pain and function relative to harms as dosages approach 90 MME per day, other treatments and effectiveness, and recommendations based on consultation with pain specialists. If patients do not experience improvement in pain and function at 90 MME or more per day, or if there are escalating dosage requirements, clinicians should discuss other approaches to pain management with the patient, consider working with patients to taper opioids to a lower dosage or to taper and discontinue opioids, and consider consulting a pain specialist.

Established patients already prescribed high dosages of opioids (≥90 MME/d), including patients transferring from other clinicians, should be offered the opportunity to reevaluate their continued use of opioids at high dosages in light of recent evidence regarding the association of opioid dosage and overdose risk. For patients who agree to taper opioids to lower dosages, clinicians should collaborate with the patient on a tapering plan.

6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed. (Recommendation category: A; evidence type: 4)

Acute pain can often be managed without opioids. When diagnosis and severity of nontraumatic, nonsurgical pain are reasonably assumed to warrant the use of opioids, clinicians should
Clinicians should not prescribe additional opioids to patients “just in case” pain continues longer than expected. Clinicians should reevaluate the subset of patients who experience severe acute pain that continues longer than the expected duration to confirm or revise the initial diagnosis and to adjust management accordingly. Clinicians should not prescribe ER/LA opioids for the treatment of acute pain.

7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids. (Recommendation category: A; evidence type: 4)

Clinicians should evaluate patients to assess benefits and harms of opioids within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation, consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased or when total daily opioid dosage is 50 MME per day or greater, and strongly consider shorter follow-up intervals (within 3 days) when starting or increasing the dosage of methadone. Clinicians should regularly reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician but taking long-term therapy, at least every 3 months and reevaluate patients exposed to greater risk of opioid use disorder or overdose (eg, patients with depression or other mental health conditions, history of substance use disorder or overdose, taking ≥50 MME/d, taking other central nervous system depressants) more frequently.

At follow-up, clinicians should determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function, whether the patient has experienced common or serious adverse events or has early warning signs of serious adverse events such as overdose (eg, sedation, slurred speech) or opioid use disorder (eg, difficulty controlling use), whether benefits of opioids continue to outweigh risks, and whether opioid dosage can be reduced or opioids can be discontinued.

Clinicians should work with patients to reduce opioid dosage or to discontinue opioids when possible if clinically meaningful improvements in pain and function are not sustained, if patients are taking high-risk regimens (eg, dosages ≥50 MME/d or opioids combined with benzodiazepines) without evidence of benefit, if patients believe benefits no longer outweigh risks or request dosage reduction or discontinuation, or if patients experience overdose or other serious adverse events or warning signs of serious adverse events.

When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal should be used. A decrease of 10% of the original dose per week is a reasonable starting point; tapering plans may be individualized based on patient goals and concerns. Slower tapers (eg, 10% per month) might be appropriate and better tolerated, particularly when patients have been taking opioids for years. More rapid tapers might be needed for patients who have overdosed on their current dosage. Clinicians should assess appropriate expertise if considering tapering opioids during pregnancy because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal. Primary care clinicians should collaborate with mental health clinicians and with other specialists as needed to optimize nonopioid pain management, as well as psychosocial support for anxiety related to the taper.

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/d), or concurrent benzodiazepine use, are present. (Recommendation category: A; evidence type: 4)

Certain risk factors can increase susceptibility to opioid-associated harms. Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing whenever possible. During pregnancy, clinicians and patients together should carefully weigh risks and benefits when making decisions about whether to initiate opioid therapy. Clinicians caring for pregnant women receiving opioids should arrange for delivery at a facility prepared to evaluate and treat neonatal opioid withdrawal syndrome. Clinicians should use additional caution and increased monitoring to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency, patients 65 years and older, and patients with anxiety or depression. Clinicians should ensure that treatment for depression and other mental health conditions is optimized, consulting with behavioral health specialists when needed. If clinicians consider opioid therapy for patients with drug or alcohol use disorders or for patients with prior nonfatal overdose, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and increase frequency of monitoring opioid therapy.

Clinicians should consider offering naloxone when prescribing opioids to patients at increased risk of overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients taking benzodiazepines with opioids, patients at risk of returning to a high dose to which they are no longer tolerant (eg, patients recently released from prison), and patients taking higher dosages of opioids (≥50 MME/d). Practices should provide education on overdose prevention and naloxone use to patients receiving naloxone prescriptions and to members of their household.

9. Clinicians should review the patient’s history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months. (Recommendation category: A; evidence type: 4)
Clinicians should review PDMP data for opioids and other controlled medications patients might have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or dangerous combinations (eg, opioids combined with benzodiazepines) that put him or her at high risk for overdose. Ideally, PDMP data should be reviewed before every opioid prescription. This is recommended in all states with well-functioning PDMPs and where PDMP access policies make this practicable (eg, clinician and delegate access permitted), but it is not currently possible in states without functional PDMPs or in those that do not permit certain prescribers to access them.

If patients are found to have high opioid dosages, dangerous combinations of medications, or multiple controlled substance prescriptions written by different clinicians, several actions can be taken to augment clinicians’ abilities to improve patient safety:

- Clinicians should discuss information from the PDMP with their patient and confirm that the patient is aware of the additional prescriptions.
- Clinicians should discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving opioids from more than 1 prescriber or receiving medications that increase risk when combined with opioids (eg, benzodiazepines).
- Clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible. Clinicians should communicate with others managing the patient to discuss the patient’s needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.
- Clinicians should calculate the total MME/d for concurrent opioid prescriptions. If patients are found to be receiving high total daily dosages of opioids, clinicians should discuss their safety concerns with the patient, consider tapering to a safer dosage, and consider offering naloxone.
- Clinicians should discuss safety concerns with other clinicians who are prescribing controlled substances for their patient.
- Clinicians should consider the possibility of a substance use disorder and discuss concerns with their patient.
- If clinicians suspect their patient might be sharing or selling opioids and not taking them, clinicians should consider urine drug testing to assist in determining whether opioids can be discontinued without causing withdrawal. A negative drug test for prescribed opioids might indicate the patient is not taking prescribed opioids, although clinicians should consider other possible reasons for this test result.

Clinicians should not dismiss patients from their practice on the basis of PDMP information. Doing so could result in missed opportunities to provide potentially lifesaving information and interventions. 10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs. (Recommendation category: B; evidence type: 4)

Prior to starting opioids for chronic pain and periodically during opioid therapy, clinicians should use urine drug testing to assess for prescribed opioids as well as other controlled substances and illicit drugs that increase risk for overdose when combined with opioids, including nonprescribed opioids, benzodiazepines, and heroin.
Clinicians should communicate with mental health professionals managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.

12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder. (Recommendation category: A; evidence type: 2)

If clinicians suspect opioid use disorder, based on patient concerns or behaviors or on findings in PDMP data or from urine drug testing, they should discuss their concerns with their patient and provide an opportunity for the patient to disclose related concerns or problems. Clinicians should assess for opioid use disorder using DSM-5 criteria. Clinicians should offer or arrange for patients with opioid use disorder to receive evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone maintenance therapy in combination with behavioral therapies). Oral or long-acting injectable naltrexone can also be used in nonpregnant adults. For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine (without naloxone) or methadone has been associated with improved maternal outcomes and should be offered.

Physicians prescribing opioids in communities without sufficient treatment capacity for opioid use disorder should strongly consider obtaining a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) that allows them to prescribe buprenorphine to treat patients with opioid use disorder. Clinicians do not need a waiver to offer naltrexone for opioid use disorder as part of their practice. Clinicians unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a substance use disorder treatment specialist, such as an office-based clinician who prescribes buprenorphine or naltrexone treatment, or from an opioid treatment program certified by SAMHSA to provide supervised medication-assisted treatment for patients with opioid use disorder.

Discussion

The evidence review focused on 5 key questions (Box 2) that have resulted in 12 recommendations (Box 5) in 3 areas: determining when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. The objective of these recommendations is to provide information about opioid prescribing for primary care clinicians treating adult patients with chronic pain.

Of primary importance, nonopioid therapy is preferred for treatment of chronic pain. Opioids should be used only when benefits for pain and function are expected to outweigh risks. Before starting opioids, clinicians should establish treatment goals with patients and consider how opioids will be discontinued if benefits do not outweigh risks. When opioids are used, clinicians should prescribe the lowest effective dosage, carefully reassess benefits and risks when considering increasing dosage to 50 MME or more per day, and avoid concurrent opioids and benzodiazepines whenever possible. Clinicians should evaluate benefits and harms of continued opioid therapy with patients every 3 months or more frequently and review prescription drug monitoring program data, when available, for high-risk combinations or dosages. For patients with opioid use disorder, clinicians should offer or arrange evidence-based treatment, such as medication-assisted treatment with buprenorphine or methadone.

Clinical guidelines complement other strategies such as strengthening the evidence base for pain prevention and treatment, reducing disparities in pain treatment, improving service delivery and reimbursement, and supporting professional and public education. To aid the application of the guideline in clinical practice, CDC is translating the guideline into user-friendly materials, such as a checklist decision aid (Figure in the Supplement), fact sheets (available at http://www.cdc.gov/drugoverdose/prescribing/resources.html), and a mobile application. CDC will also work with partners to support clinician education on pain management options, opioid therapy, and risk mitigation strategies. Efforts that might enhance implementation of recommended practices include development of quality improvement measures, implementing clinical decision support, and integrating initiatives to promote safer prescribing within insurance plans. In addition, policy initiatives that address barriers to implementation of the guideline, such as increasing accessibility of PDMP data, e-prescribing, and availability of clinicians who can offer medication-assisted treatment for opioid use disorder are strategies to consider to enhance implementation of the recommended practices. CDC will work with federal partners and payers to evaluate strategies such as payment reform and health care delivery models that could improve patient health and safety. For example, strategies might include strengthened coverage for nonpharmacologic treatments, appropriate urine drug testing, and medication-assisted treatment; reimbursable time for patient counseling; and payment models that improve access to interdisciplin ary, coordinated care.

The CDC guideline provides recommendations that are based on best available evidence, interpreted and informed by expert opinion. Evidence informing the recommendations is based on observational studies or randomized clinical trials with notable limitations, as well as clinical experience and observations, characterized as low in quality under GRADE methodology. As highlighted by a National Institutes of Health expert panel, "evidence is insufficient for every clinical decision that a provider needs to make about the use of opioids for chronic pain." The expert panel recommended that research is needed to improve current understanding of which types of pain, specific diseases, and patients are most likely to be associated with benefit and harm from opioid pain medications; evaluate and estimate cost-benefit of multidisciplinary pain interventions; develop and validate tools for identification of patient risk and outcomes; assess the effectiveness and harms of opioid pain medications with alternative study designs; and investigate risk identification and mitigation strategies and their effects on patient and public health outcomes.

To inform future guideline development, more research is needed to fill critical evidence gaps. Yet given that chronic pain is a significant public health problem, the risks associated with long-term opioid therapy, the availability of effective alternative treatment options for pain, and the potential for improvement in the quality of health care with the implementation of recommended practices, a guideline for prescribing is warranted with currently available evidence. The balance between benefits and harms of long-
term opioid therapy for chronic pain based on both clinical and contextual evidence is sufficiently clear to support the issuance of category A recommendations in most cases.

Conclusions

The guideline is intended to improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death. CDC is committed to evaluating the guideline to identify effects on clinician and patient outcomes, both intended and unintended, and will revisit the guideline to determine if evidence gaps have been sufficiently addressed to warrant an update of the guideline and revise the recommendations in future updates when warranted.

REFERENCES


Clinical Review & Education Special Communication

Clinical Review & Education Special Communication


January 12, 2016

Thomas Frieden, MD, MPH  
Director  
Centers for Disease Control and Prevention  
1600 Clifton Road  
Atlanta, GA  30329-4027

Re:  Docket No. CDC-2015-0112; Proposed 2016 Guideline for Prescribing Opioids for Chronic Pain

Dear Dr. Frieden:

On behalf of our physician and medical student members, the American Medical Association (AMA), the largest physician organization in the U.S., appreciates the opportunity to review and comment on the Centers for Disease Control and Prevention’s (CDC) Proposed Guideline for Prescribing Opioids for Chronic Pain. We commend CDC’s decision to open up a period of public comment to allow a broader group of important stakeholders the opportunity to provide their unique perspectives on the public health challenges related to the intersection of pain management, prescription opioid use, and opioid diversion, misuse, and unintentional overdose.

The AMA shares with CDC the goal of reducing the burden of harm from controlled substances, including opioid analgesics. The individual and family tragedies and societal costs attributable to opioid-related overdose, emergency department visits, deaths, and addiction are deeply concerning. To make meaningful progress towards ending this epidemic, a broad-based public health approach is required. This approach must balance patients’ needs for comprehensive pain management services, including opioid analgesics when clinically appropriate, with efforts to promote appropriate prescribing, reduce diversion and misuse, promote an understanding that substance use disorders are chronic conditions that respond to treatment, and expand access to treatment for individuals with substance use disorders.

As it has done in addressing so many other serious epidemics, the AMA applauds CDC for treating the epidemic of opioid overdose deaths as a high priority. We continue to recommend that CDC’s efforts in this area be aligned with those of other federal partners, including the White House and its Office of National Drug Control Policy, the Interagency Pain Research Coordinating Committee and its National Pain Strategy, the National Institute on Drug Abuse, the Substance Abuse and Mental Health Services Administration, the Department of Health and Human Services, and the U.S. Surgeon General. The White House initiative announced in October 2015 is designed to forge a collaborative effort involving multiple stakeholders in the medical community working towards a single set of measurable objectives. This collaborative effort includes commitments from the AMA, the American Dental Association, and the American Osteopathic Association, as well as other medical specialty societies and state medical associations. In a separate effort to engage the physician community more directly to implement solutions to opioid misuse and harm, the AMA formed a Task Force of national medical specialty society
and state medical association partners to promote appropriate pain care and reduce opioid-related harm by encouraging physicians to register for and consult their state’s prescription drug monitoring program, access available high quality educational offerings intended to reduce opioid misuse and harm, expand the use of naloxone, and reduce the stigma commonly experienced by patients with chronic pain or substance use disorders (www.ama-assn.org/go/endopioidabuse).

GENERAL COMMENTS ON CDC METHODS AND RECOMMENDATIONS

While the discussion under several of the specific draft recommendations has been revised and/or amplified based on designated stakeholder input and provides additional clarity, the recommendations themselves are largely unchanged from the initial draft. Accordingly, while the AMA supports many of the recommendations, we continue to have serious concerns that some either contain a degree of specificity not supported by the existing evidence or conflict with official Food and Drug Administration (FDA)-approved product labeling for opioid analgesic products. It seems incongruous that virtually all of the specific guidelines carry a graded recommendation that CDC believes should “apply to all patients with chronic pain and that…most patients should receive the recommended course of action,” given the limitations of the evidence, especially where CDC experts’ opinions are the essential foundation for the recommendation.

States regulate the practice of medicine and many already have adopted opioid prescribing guidelines that were developed by a coalition of state-based stakeholders, including physicians and other health care professionals, public health officials, patients and patient advocates, and policy makers working together to ensure balance. The low or very low quality of evidence supporting the proposed CDC guidelines has the potential to create considerable confusion in the states. While CDC has acknowledged that the guidelines are advisory in nature and they do not intend for state legislators, professional licensing boards, hospitals, insurers, courts, or others to “officially” implement or follow specific elements of the guidelines, this is not a practical or realistic expectation given the national respect that comes with a guideline issued by CDC. Accordingly, concerns remain about potential unintended consequences for patients depending on how specific elements of the guidelines (as written) may be interpreted, implemented, or enforced. Some patients with chronic pain who have maintained functional improvement on stable opioid doses are already experiencing difficulties in keeping their current source of care and/or finding physicians who are willing to treat them.

While the summary and introductory discussion acknowledge that “the guideline does not focus broadly on pain management,” and “it is important that patients receive appropriate pain treatment,” the guideline otherwise lacks a patient-centric view, other than to note that for patients who are already maintained on “high opioid dosages,” “providers should empathetically review benefits and risks of continued high dose opioid therapy and should offer to work with the patient to taper opioids to safer dosages.” Although the guideline is expressly focused on prescribing opioids for chronic pain, by crafting the first recommendation as “nonpharmacologic and nonopioid pharmacologic therapies are preferred for chronic pain,” CDC cannot disavow an obligation to frame the pain management discussion in a balanced fashion. The AMA, therefore, asks that CDC include patient advocates in its formal review of these and other comments to ensure that patient needs are adequately addressed.

Although population-level data may be relied on to help construct clinical guidance, pain is an intensely personal and conscious experience influenced by emotion, cognition, memory, interpersonal and social
context, and other factors. Patient-reported intensity of pain may not correlate with the magnitude or identifiable source of injury. Because objective tests for pain intensity (or even the presence or absence of pain) are still at a rudimentary stage of development, the best clinical approach in most circumstances is to assume that the patient is reporting a true experience. Accepting a patient’s complaint of pain as valid does not require clinical identification of a physical cause, or demand the initiation of a specific treatment. It does, however, provide a foundation for assessment and the basis for developing an effective patient-physician dialogue and an approach to individualized, patient-centered treatment. Meaningful and appropriate treatments are best achieved via shared decision-making. Health disparities in pain management and legitimate access to opioid analgesics for acute pain remain evident, and clinically relevant differences in pain expression and responsiveness based on sex, race/ethnicity, and genetic constitution also exist. Based on feedback from patient groups, patients suffering from chronic pain increasingly view themselves as collateral damage in efforts to restrict opioid prescribing decisions via state-based regulations and legislative mandates, and are fearful of the potential effect these guidelines may have on access for patients with legitimate medical needs. It is important that this not be an unintended consequence of this process. Accordingly, the proposed guideline could be substantially improved by incorporating some fundamental acknowledgements that many patients experience persistent pain that is not well controlled, substantially impairs their quality of life and/or functional status, stigmatizes them, and could be managed with more compassionate patient care. The National Pain Strategy has acknowledged that clinician biases and negative attitudes towards pain negatively affect the care and services they provide to patients.

The AMA has great respect for the core mission and activities of CDC that are designed to protect the health of the public. Individuals from a variety of disciplines and settings with specific expertise were chosen for the expert panel, a reflection of the challenges faced in trying to address this complex public health issue in a balanced fashion. The expert panel was charged with the most significant assignment in this process. It appears, however, that only a limited number of clinicians who are actively managing chronic pain patients were included. While it is necessary to integrate various disciplines because of the complex nature of prescription drug misuse and addiction, the process moving forward would benefit from a balanced Advisory Committee that includes patient advocates, as well as clinicians from various medical specialty and practice settings representing a diverse set of views and experiences in treating chronic pain and opioid use disorder, and limiting participation of individuals aligned with public policies that may have a predictable effect on the recommendations. This type of approach is even more important when the evidence-base is limited, thereby requiring a consensus-type approach and the use of “expert opinion.” The AMA asks, therefore, that before commencing with the formal review and consideration of revisions submitted by stakeholders, CDC broaden the Advisory Committee by inviting patient advocates and clinicians, including physicians, pharmacists, and dentists, who treat a broad base of patients with pain. The AMA would be pleased to recommend physicians from member organizations of the AMA Task Force to Reduce Opioid Abuse to help accomplish this.

Finally, the change in terminology from “low quality” or “very low quality” evidence to category 3 or 4 evidence is not helpful to the reader and primarily serves to camouflage the criticism derived from issuing “strong” recommendations based on low quality evidence. Because the guidelines may eventually be used by a broad range of stakeholders as described earlier, the AMA recommends that CDC clearly identify the quality of the evidence used by returning to the easily understandable and common sense language used in the original draft.
SPECIFIC COMMENTS ON CDC RECOMMENDATIONS

Recommendation #1

Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Providers should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks to the patient (recommendation category A, evidence type 3).

Expansion of the discussion on various non-opioid pharmacologic therapies is a helpful revision. Clearly, the use of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) for musculoskeletal pain, and certain antiepileptic or antidepressant drugs for neuropathic pain are well established treatments. While it is true that NSAIDs can be helpful for mild-moderate musculoskeletal pain, the risks associated with both the acute and chronic use of these drugs should not be minimized. Much attention has been devoted to limiting the use of NSAIDs to the lowest dose for the shortest duration of time (Alliance for Rational Use of NSAIDs; http://nsaidalliance.com).

The evidence review concludes that “several non-pharmacologic and non-opioid pharmacological treatments have been shown to be effective in managing chronic pain.” The evidence presented for the effectiveness of non-pharmacologic approaches focuses on cognitive behavioral therapy (CBT), exercise therapy, and integrative multimodal therapies. While some modest short-term effects are apparent, none of these studies are sufficient to conclude that such approaches can be widely implemented and are effective for long-term use. Broad-based, effective implementation would require large scale changes in the public and private payer communities and better evidence to inform the most effective non-pharmacologic approach for various chronic pain conditions.

Furthermore, access to non-pharmacologic and non-opioid pharmacological treatments and reimbursement for them are often inadequate, especially for multidisciplinary care (http://www.painmed.org/files/minimum-insurance-benefits-for-patients-with-chronic-pain.pdf). The National Pain Strategy specifically identifies that a pressing need exists to assess insurer practices such as prior authorization, step therapy, fail-first protocols, specialty tier payment structures, and other limits on reimbursement for multidisciplinary care treatments that act as barriers to effective care. Moreover, it is not clear how many primary care clinicians (the target audience of these guidelines) are proficient in offering important non-pharmacologic approaches, including mindfulness, focused imagery, biofeedback, relaxation, or CBT, which at its most comprehensive implementation requires a multidisciplinary approach performed by various experts. This recommendation may be interpreted as requiring a “fail-first” approach of all available treatments for chronic pain before opioids should even be considered. We ask that CDC clarify that it does not support fail-first protocols or other policies meant to inhibit access to care, especially for serious illnesses and conditions such as chronic pain.

We also reiterate our concerns about the evidence base used to inform the guidelines. It is not clear from the discussion whether the standard for the non-pharmacologic and non-opioid pharmacological treatments also required randomized trials with study duration of one year to be included in the efficacy analysis. The methodology description notes that evidence for the guideline built on systematic reviews conducted in 2009 and 2014, with an update of the 2014 review. However, the inclusion criteria for opioid efficacy studies were changed from a best evidence approach in 2009 to a one-year, randomized
trial requirement. The same standard was not applied to the measurement of harms, nor apparently to the non-opioid based therapies. The same standard should be applied to all treatments that are being evaluated for efficacy for chronic pain and for which the guidelines state or conclude they are effective, and the analysis and discussion should be revised to reflect that approach.

Therefore, we recommend the following revisions to Recommendation #1. This recommendation is not implementable without the corresponding responsibilities of payers being addressed.

**Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Providers should only consider adding using opioid therapy if expected benefits for both pain and/or function are anticipated to outweigh risks. In order to achieve this goal, public and private payer policies must be fundamentally altered and aligned to support payment for non-pharmacologic treatments and multimodal care. In addition, more evidence must be developed to inform clinical decision-making on the use of non-pharmacologic approaches, and more clinicians need to be trained in their effective use.**

**Recommendation #2**

**Before starting long-term opioid therapy, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should not initiate opioid therapy without consideration of how therapy will be discontinued. Providers should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (recommendation category: A, evidence type: 4).**

While we generally support this recommendation, some situations exist where patients may have intractable pain and sufficient disability such that functional improvement is not possible, and relief of pain and suffering is a supportable primary goal. This is noted in the revised discussion. In an analogous fashion, some patients may demonstrate functional improvement, with limited changes in pain scores. We find the discussion about the nuances of acute pain, chronic pain, prescription length, and corresponding evidence disconnected. Prescribers are advised to make decisions regarding the appropriateness of opioid therapy based on common definitions of chronic pain (>3 months or beyond the time of normal tissue healing, which could be significantly shorter than 3 months) and potential uncertainty in the transition from acute to chronic pain, but the evidence review disregards any opioid-based studies (albeit low or very low quality evidence) less than one year in duration. Because both pain and function may not improve in responsive patients, and “treatment goals” are the grounding element, we recommend the following revisions to Recommendation #2.

**Before starting long-term opioid therapy, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should not initiate long-term opioid therapy without consideration of how therapy will be discontinued if benefits do not exceed risks. Providers should continue opioid therapy only if there is clinically meaningful improvement in treatment goals pain and function that outweighs risks to patient safety.**
Recommendation #3

Before starting and periodically during opioid therapy, providers should discuss with patients known risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy (recommendation category: A, evidence type: 3).

We generally support this recommendation, although it introduces a modifying term for benefits (realistic) that does not appear elsewhere. The additional considerations regarding use in patients who are cognitively impaired and directions to secure safe storage are helpful additions. With respect to discussion about “fatal overdose,” it may be helpful to better explain that the real concern is respiratory depression to perhaps facilitate better recognition of its occurrence. Taken one by one, the points of emphasis have varying levels of merit, but taken together they must be implemented in a patient-centered way, on an individual basis, and in a manner that does not promote stigma or adversely affect the patient-physician relationship. This list, moreover, is an example of the type of list that will likely be relied upon by others in creating new requirements for physicians who treat patients with pain.

The AMA also asks, therefore, that specific language preceding the list be revised to read as follows: Providers are encouraged to have open and honest discussions with their patients so as to avoid stigmatizing the decision to start, continue, or discontinue opioids or non-opioid therapy. Providers should do the following. Considerations for providers include the following:

Recommendation #4

When starting opioid therapy, providers should prescribe short-acting opioids instead of extended release/long-acting (ER/LA) opioids.

We generally support this recommendation. We also note that this section raises considerable concern about the use of methadone and transdermal fentanyl. This may be an opportunity for CDC to work with the FDA and others to help promote education for clinicians on the appropriate use of these two long-acting, extended release products. The AMA stands ready to promote such education. Overall, the AMA is pleased that CDC relies on the FDA-approved labeling of ER/LA opioids for guidance under this recommendation. While it is true that abuse deterrent formulations do not prevent opioid misuse through oral intake or unintentional overdose through this route, they are less subject to product manipulation. Interestingly, the expert panel was unable to affirm any value in the clinical use of these formulations, despite the fact that virtually all product approvals in this category will have this expectation moving forward.

Recommendation #5

When opioids are started, providers should prescribe the lowest possible effective dosage. Providers should use caution when prescribing opioids at any dosage, should implement additional precautions when increasing dosage to > 50 morphine milligram equivalents (MME)/day and should generally avoid increasing dosages to > 90 MME/day.

We agree with the recommendation to prescribe the lowest effective dose. This recommendation is not unique to clinical decisions on pain management, but is a general tenet of designing a dosage regimen and
treatment plan. However, in contrast to the discussion of the clinical role of ER/LA opioids, this recommendation is in direct conflict with approved product labeling for the clinical use of opioid analgesics and the findings of the recent review by the FDA regarding clinical decision algorithms based on daily MME. A variety of prescriber behaviors, patient/user behaviors and characteristics, and environmental and systemic determinants exist that contribute to opioid overdose mortality. These factors may operate independently but interact in complex ways according to geography and population (King NB et al. Am J Public Health. 2014 Aug; 104(8):e32-42). Accordingly, preventing additional opioid-related mortality will require interventions that address multiple determinants that are tailored to specific locations and populations. In addition, the language of this recommendation is vague and open to wide interpretation. What constitutes “caution” when using any dose? What additional precautions should be taken when increasing a daily dose above 50 MME?

As a result, this recommendation as currently stated has the potential to cause confusion, uncertainty, and conflicting institutional or state policies that may have unintended consequences. One likely consequence is that most insurers and other payers will use this recommendation to deny or impose new hurdles to coverage of any dose that exceeds the threshold. Another likely consequence is that patients experiencing pain who require a daily dose above 50 MME will face additional prejudice and stigma. While several states have enacted laws or regulations designed to modify clinical decision-making based on MMEs, analysis of the actual efficacy of these approaches and their effect on reducing overdose and pain management is lacking, including whether they may have unintended consequences (Ziegler SJ. Pain Medicine, 2015). In states that have adopted MME thresholds, prescribers appear to modify behavior to avoid specific sanctions and/or the need for additional action steps. The effects on patients have not been quantified. New data from Ohio, which has an 80 mg MME threshold, demonstrate that fewer high dose prescriptions were issued and the number of prescriptions was reduced overall, but death rates due to opioids, and in particular heroin, continued to rise. The reliance on expert opinion throughout this section, the existing multitude of state MME thresholds, and the absence of MME thresholds from the current product labeling for opioid analgesics coupled with a high degree of variability in patient responsiveness to opioids and uncertainty in morphine equivalent calculators, argue against establishing a bright line for clinical decision-making based solely on this variable.

The AMA asks, therefore, that this recommendation either be reconsidered in its entirety, or that the focus be redirected to encouraging use of the lowest possible effective dose, with any dose escalation based on clinical response and the existence of continued improvement in pain and function. This could be accomplished by revising recommendation #2 to read as follows:

**Before starting long-term opioid therapy, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should initiate opioid therapy with the lowest effective dose. Continued opioid therapy and/or dose escalation should occur only if there is clinically meaningful improvement in treatment goals pain and function that outweighs risks to patient safety.**

**Recommendation #6**

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, providers should prescribe the lowest effective dose of short-acting opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to
require opioids. Three or fewer days will usually be sufficient for non-traumatic pain not related to major surgery (recommendation category: A, evidence type 4).

The three-day limit imposed by this recommendation in the outpatient setting is arbitrary and the surrounding circumstances are clinically vague. If this recommendation is targeting post-surgical prescriptions (which would deviate from the stated goal of the guidelines to apply to primary care), then an effort should be made to provide the supporting evidence base. What is the definition of “major surgery”? The referenced clinical practice guidelines from emergency department protocols or “bridge” prescriptions for a three-day limit are prudent and widely supported, but are not applicable in a broad-based fashion to all scenarios of acute pain. States that have supported limits on opioid analgesics prescribed in the emergency department have largely done so to allow the patient sufficient time to follow-up with their primary care provider or other physician managing the patient’s chronic pain, and not as a clinical recommendation based on anticipated healing time or duration of pain sufficient to require an opioid analgesic. Nevertheless, we strongly support messaging about the need to conservatively tailor the number of pills per prescription for acute pain. We believe this can be accomplished by modifying this recommendation to read as follows (with the various clinical guidance of three to 14 days appearing in the supporting narrative discussion):

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, providers should prescribe the lowest effective dose of short-acting opioids and should prescribe no greater in a quantity than needed only for the expected duration of pain severe enough to require opioids, and not based on prescriber or patient convenience. Three or fewer days will usually be sufficient for non-traumatic pain not related to major surgery.

Recommendation #7

Providers should evaluate patients within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation to assess benefits and harms of continued opioid therapy. Providers should evaluate patients receiving long-term opioid therapy every 3 months or more frequently for benefits and harms of continued opioid therapy. If benefits do not outweigh harms of continued opioid therapy, providers should work with patients to reduce opioid dosage and to discontinue opioids when possible (recommendation category: A, evidence type: 4).

We agree with the need to appropriately monitor patients during the onset of long-term therapy or after dosage escalation, but recommend that CDC pay close attention to comments received from various medical specialty societies, including those in the stakeholder review panel, to address the specific timeframes that might comprise this recommendation. While it may be somewhat nuanced, the last sentence in this recommendation does not accommodate a clinical situation where reducing the opioid dose may restore an appropriate risk/benefit ratio. The AMA asks, therefore, that the last sentence should be revised to read as follows:

If benefits do not outweigh harms of continued opioid therapy, providers should work with patients to reduce opioid dosage and, if necessary, to discontinue opioids to prevent harm when possible.
Recommendation #8

Before starting and periodically during continuation of opioid therapy, providers should evaluate risk factors for opioid-related harms. Providers should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, or higher opioid dosages (≥50 MME), are present (recommendation category: A, evidence type: 4).

We agree with the language presented in recommendation #8 as a prudent clinical approach, as well as the guidance offered on expanding the use of naloxone. However, this recommendation is somewhat redundant with others, such as #1, #2, #3, and #7 that also urge a consideration of benefits versus risks. Because the evidence review concludes that primary care physicians are not well equipped to assign risk profiles, commonly recommended screening instruments do not work, and physicians already have heightened concerns and misgivings about managing patients with chronic pain and prescribing opioid analgesics, additional clarity about CDC’s intent for this recommendation is needed.

The supporting text concerning risk factors identifies patients with sleep-disordered breathing, women of reproductive age, pregnant women, and patients with renal or hepatic insufficiency, patients aged over 65 years, patients with mental health conditions and those receiving benzodiazepines, and patients with substance use disorder. Otherwise, providers are: 1) directed to ask patients about drug and alcohol use, use Prescription Drug Monitoring Programs (PDMP) data and drug testing as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and/or overdose; 2) advised to counsel patients on increased risks of overdose when opioids are combined with other drugs or alcohol; and, 3) directed to ensure that patients receive effective treatment for substance use disorders when needed. The AMA is concerned with aspects of this section that may cause additional stigma to a patient who benefits from opioid therapy. The reactions of state legislatures to neonatal abstinence syndrome demonstrate the significant challenges in crafting hardline policies that would apply to every patient. In no case should a pregnant woman be treated as a criminal if she and her physician determine that opioids are needed, but that is how some policymakers have approached this clinical determination. In addition, a woman in pain deserves to have her pain treated; if the benefits of opioids outweigh the risks of harm, then that decision should be respected. CDC’s discussion needs to more fully reflect this delicate balance. Furthermore, significant knowledge gaps exist regarding the use and interpretation of urine testing, as well as payment barriers. It may be helpful to identify specific questions (or line of questioning) in the supporting discussion that would comprise adequate history taking for alcohol and drug use.

Recommendation #9

Providers should review the patient’s history of controlled substance prescriptions using state PDMP data to determine whether the patient is receiving excessive opioid dosages or dangerous combinations that put him/her at high risk for overdose. Providers should review PDMP data when starting opioid therapy and periodically during long-term opioid therapy, ranging from every prescription to every 3 months (recommendation category: A, evidence type: 4).

We strongly agree with the need for physicians and other prescribers to register for and access their state-based PDMP when clinically appropriate. This is a primary goal of the AMA Task Force. We appreciate
that CDC recognizes the sometimes significant barriers to PDMPs being more widely used by physicians. The AMA has long advocated for reauthorization and full funding of National All Schedules Prescription Electronic Reporting Act, and we work regularly with state medical associations to advocate for stable funding streams for state PDMPs. Furthermore, we are pleased to see that CDC also recognizes that some patients may suffer unintended consequences by being discharged from the practice. Specifically, the AMA notes that CDC and several states have publicized decreases in the incidence of individuals who would qualify as “doctor shoppers.” Data are lacking about the characteristics of these individuals, and uncertainties remain about what happens to them after they are identified. For example, some may be receiving multiple controlled substances from multiple providers because of fragmented care in need of coordination (e.g., Medicare Part D beneficiaries). Some are in need of treatment for an opioid use disorder, and some may be promptly discharged from the practice and be at risk for seeking illicit substances. While PDMPs can help identify patients receiving multiple prescriptions from multiple prescribers or dispensers, and this behavior is a risk factor for unintentional overdose, we believe the steps to be taken after identifying such individuals are much more complex and require further research and attention. While it is an important variable to quantify, one should not be satisfied with concluding that PDMP data were used to reduce doctor shopping; further examination of what happens to these individuals is warranted. We defer to the medical specialty society stakeholders to comment on the appropriate triggers for how often a PDMP should be consulted, and in the absence of consensus, the AMA recommends the following revisions to Recommendation #9. As with Recommendation #3, consider using the term “respiratory depression” rather than overdose.

**Recommendation #10**

When prescribing opioids for chronic pain, providers should use urine drug testing before starting opioids therapy and consider urine drug testing at least annually for all patients on long-term opioid therapy to assess for prescribed medications as well as other controlled substances and illicit drugs (recommendation: B, evidence type: 4).

We note that the evidence review relied on by CDC does not support the conclusion that urine drug testing improves outcomes in patients receiving opioids for chronic pain. Nevertheless, it is one objective measure that can be used as part of a broader risk mitigation strategy when designing treatment and monitoring strategies for individual patients on chronic opioid therapy. The decision on how and when to use urine drug testing for individual patients should be left up to the treating physician. This recommendation offers another example of where the AMA agrees with CDC’s intent, but the practical implications need to be more adequately addressed. Significant knowledge gaps exist regarding the use of interpretation of urine drug tests in primary care and different monitoring frequencies may be required based on individual patient variables. Furthermore, the wide variability in insurance coverage is not insignificant, with implications for physician reimbursement for interpretation, to the potential costs for both private and public payer systems. Of equal, if not more significance, is the fact that many patients currently have to pay for urine testing out of pocket, which may impact their ability to comply with a pain
care agreement. Because consensus is lacking on this issue, the AMA recommends the following revisions to Recommendation #10:

**When prescribing opioids for chronic pain, providers should use urine drug testing before starting chronic opioids therapy and consider urine drug testing periodically at least annually for all patients on long-term opioid therapy to assess for prescribed medications as well as other controlled substances and illicit drugs.**

Recommendation #11

**Providers should avoid prescribing of opioid pain medication and benzodiazepines concurrently whenever possible (recommendation category: A, evidence type: 3).**

Benzodiazepines are a co-occurring substance in a substantial minority of patients who suffer an opioid-related overdose, just as they are commonly used by other individuals as a pattern of polysubstance abuse. Therefore, we prefer that the language be framed in a way that recognizes the clinical-decision making authority of the treating physician, to read as follows:

**Providers should avoid prescribing of opioid medication and benzodiazepines concurrently whenever possible, unless it is clinically indicated and required for optimal patient management.**

Recommendation #12

**Providers should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (recommendation category: A, evidence type: 3).**

We support this recommendation. While the recommendation focuses on opioid agonist treatment in combination with behavioral therapies, patients also may respond to naltrexone (as noted in the discussion) and some may respond to abstinence-based approaches; perhaps the latter also can be noted in the narrative. However, the ability of primary care physicians to “ensure that patients get treatment for opioid use disorder when needed” is severely constrained by a lack of access to treatment and numerous public and private payer policies that are based on a lack of understanding that addiction is a chronic brain disease. Accordingly, we urge that this recommendation be revised to read as follows:

**Providers should offer or arrange evidence-based treatment (usually opioid agonist treatment in combination with behavioral therapies) for patients with opioid use disorder. In order to achieve this goal, more physicians need to be trained in providing direct patient care for individuals with opioid use disorder, and government funding, as well as public and private payer policies, must be fundamentally altered and aligned in support of expanded access to treatment. In addition, efforts should be directed at reducing the stigma associated with substance use disorders and raising awareness that addiction is a chronic brain disease.**

The AMA appreciates the opportunity to review and comment on this important issue. We sincerely hope that CDC will seize the opportunity to align itself with other ongoing efforts designed to foster a balanced, public health-based approach to improving pain management practices while minimizing the
diversion of controlled substances, reducing unintentional overdoses and deaths from opioid analgesics, and supporting improved access to treatment for patients with substance use disorders.

Sincerely,

James L. Madara, MD

cc: Deborah Dowell, MD, MPH