CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016

Prepared by:
Deborah Dowell, MD from the Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC
Tamara M. Haegerich, PhD from the Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC
Roger Chou, MD from Oregon Health and Science University

Summary

This guideline provides recommendations for primary care providers who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses 1) when to initiate or continue opioids for chronic pain; 2) opioid selection, dosage, duration, follow-up, and discontinuation; and 3) assessing risk and addressing harms of opioid use. CDC developed the guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, and recommendations are made on the basis of a systematic review of the scientific evidence while considering benefits and harms, values and preferences, and resource allocation. CDC consulted with experts knowledgeable in the areas of opioid prescribing, addiction, substance use disorder treatment, and pain management to interpret the evidence and inform the recommendations and provided opportunities for stakeholder review, constituent engagement, and peer review. It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. This guideline 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 abuse, dependence, overdose, and death.

Introduction

Background

Opioids are commonly prescribed for pain. An estimated 20% of patients presenting to physician offices with noncancer pain symptoms or pain-related diagnoses (including acute and chronic pain) receive an opioid prescription (*1*). In 2012, health care providers wrote 259 million prescriptions for opioid pain medication, enough for every adult in the United States to have a bottle of pills (*2*). Opioid prescriptions per capita increased 7.3% from 2007 to 2012, with opioid prescribing rates increasing more for family practice, general practice, and internal medicine compared with other specialties (*3*). Rates of opioid prescribing vary greatly across states in ways that cannot be explained by the underlying health status of the population, highlighting the lack of consensus among providers on how to use opioid pain medication (*2*).

Prevention, assessment, and treatment of chronic pain are challenges for health providers and systems. Pain might go unrecognized, and patients can be at risk for inadequate pain treatment, particularly racial and ethnic minorities, women, the elderly, persons with cognitive impairment, and those with cancer and at the end of life. (*4*). Patients should receive appropriate pain treatment based on a careful consideration of the benefits and risks of treatment options. Chronic pain has been variably defined but is considered within this guideline as pain that typically lasts >3 months or past the time of normal tissue healing (*5*). Chronic pain can be the result of an underlying medical disease or condition, injury, medical treatment, inflammation, or an unknown cause (*4*). Estimates of the prevalence of chronic pain vary, but it is clear that the number of persons experiencing chronic pain in the United States is substantial. The 1999–2002 National Health and Nutrition Examination Survey estimated a prevalence of current widespread or localized pain lasting at least 3 months of 14.6% (*6*). The overall prevalence of common, predominantly musculoskeletal pain conditions that can be chronic (e.g., arthritis, rheumatism, chronic back or neck problems, and frequent severe headaches) was estimated at 43% among adults in the United States (*7*) based on a survey conducted during 2001–2003. Most recently, analysis of data from the 2012 National

DRAFT

Health Interview Study revealed an estimated prevalence of daily pain of 11.2% (*8*). It is hard to estimate the number of persons who could potentially benefit from opioid pain medication long term. Although evidence supports short-term efficacy of opioids for reducing pain and improving function in noncancer nociceptive and neuropathic pain in trials lasting <16 weeks (*9*), few studies to assess the long-term benefits of opioids for chronic pain (pain lasting >3 months) with outcomes examined at least 1 year later have been conducted (*10*). On the basis of data available from health systems, researchers estimate that 9.6 to 11.5 million adults, or approximately 3%–4% of the adult U.S. population, were prescribed long-term opioid therapy in 2005 (*11*).

Opioid pain medication use presents serious risks, including opioid use disorder (opioid abuse or dependence, sometimes referred to as addiction) and overdose. Since 1999, more than 140,000 persons have died from overdose related to opioid pain medication in the United States (*12*). In the past decade, while the death rate for the top leading causes of death such as heart disease and cancer has decreased substantially, the death rate associated with opioid pain medication has increased substantially (*13*). More than 16,000 deaths occurred in 2013, four times the number of overdose deaths related to these drugs in 1999 (*12*). Sales of opioid pain medication have increased in parallel with opioid-related overdose deaths (*14*). The Drug Abuse Warning Network estimated that >420,000 emergency department visits were related to the misuse or abuse of narcotic pain relievers in 2011, the most recent year for which data are available (*15*). While clinical criteria have varied over time, opioid use disorder is a problematic pattern of opioid use leading to clinically significant impairment or distress. This disorder is manifested by specific criteria such as unsuccessful efforts to cut down or control use and use resulting in social problems and a failure to fulfill major role obligations at work, school, or home (*16*). In 2013, an estimated 1.9 million persons abused or were dependent on prescription opioid pain medication (based on DSM-IV criteria) (*17*). Having a history of a prescription for an opioid pain medication increases the risk for overdose and opioid use disorder (*18–20*), highlighting the value of guidance on safer prescribing practices for providers.

This guideline provides recommendations for the prescribing of opioid pain medication by primary care providers for chronic pain (i.e., pain conditions that typically last longer than 3 months or past the time of normal tissue healing) in outpatient settings outside of active cancer treatment, palliative care, and end-of-life care. Although the guideline does not focus broadly on pain management, appropriate use of long-term opioid therapy must be considered within the context of all pain management strategies (including nonopioid pain medications and nonpharmacologic treatments). Recommendations are based on a systematic review of the best available evidence, along with consultation from an expert panel. The guideline is intended to ensure that providers and patients consider safer and more effective treatment, improve patient outcomes such as pain and function, and reduce the number of persons who develop opioid use disorder, overdose, or experience other adverse events related to these drugs. The guideline offers recommendations rather than prescriptive standards; providers should consider the circumstances and unique needs of each patient.

Rationale

Primary care providers 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 (*21*). Across specialties, physicians believe that opioid pain medication can be effective in controlling pain but agree that physical dependence, tolerance, and addiction are common consequences of prolonged use; nevertheless, long-term opioid therapy often is overprescribed for patients with chronic noncancer pain (*22*). These attitudes and beliefs, combined with increasing trends in opioid use disorder and opioid-related overdose, underscore the need for better provider guidance on opioid prescribing. Clinical practice guidelines focused on prescribing can improve provider knowledge, change prescribing practices (*23*), and ultimately benefit patient health.

DRAFT

Professional organizations, states, and federal agencies have developed guidelines on opioid prescribing (e.g., the American Pain Society/American Academy of Pain Medicine, 2009; the Washington Agency Medical Directors Group, 2015; and the U.S. Department of Veterans Affairs/Department of Defense, 2010) (*24–26*). Existing guidelines share some common elements, including dosing thresholds, cautious titration, and risk mitigation strategies such as using risk assessment tools, treatment agreements, and urine drug testing. However, there is considerable variability in the specific recommendations (e.g., range of dosing thresholds of 90 morphine milligram equivalents (MME)/day to 200 MME/day), audience (e.g., primary care providers versus specialists), use of evidence (e.g., systematic review versus expert opinion), and rigor of methods for addressing conflict of interest (*27*). Most guidelines, especially those that are not based on evidence from scientific studies published in 2010 or later, also do not reflect the most recent scientific evidence about risks related to opioid dosage.

This CDC guideline offers clarity on recommendations based on the most recent scientific evidence, informed by expert opinion, with stakeholder and constituent input considered. Scientific research has identified high-risk prescribing practices that have contributed to the overdose epidemic (e.g., high-dose prescribing, overlapping opioid and benzodiazepine prescriptions, and extended-release/long-acting [ER/LA] opioids for acute pain) (*20*,*28*,*29*). Using guidelines to address problematic prescribing has the potential to optimize care and improve patient safety based on evidence-based practice (*23*), as well as reverse the cycle of opioid pain medication abuse that contributes to the overdose epidemic.

Scope and Audience

This guideline is intended for primary care providers (e.g., family physicians and internists) who are treating patients with chronic pain (i.e., pain lasting >3 months or past the time of normal tissue healing) in outpatient settings. Prescriptions by primary care providers account for nearly half of all dispensed opioid prescriptions, and the growth in prescribing rates among these providers has been above average (*3*). Although the transition from use of opioid therapy for acute pain to chronic pain is hard to predict and identify, the guideline is intended to inform providers who are considering prescribing opioid pain medication for painful conditions that can or have become chronic.

This guideline is intended to apply to patients aged ≥18 years with chronic pain outside of palliative and end-of-life care. For this guideline, palliative care is defined in a manner consistent with that of the Institute of Medicine as care that provides relief from pain and other symptoms, supports quality of life, and is focused on patients with serious advanced illness. Palliative care can begin early in the course of treatment for any serious illness that requires excellent management of pain or other distressing symptoms (*30*). End-of-life care is defined as care for persons with a terminal illness or at high risk for dying in the near future in hospice care, hospitals, long-term care settings, or at home. Patients within the scope of this guideline include cancer survivors with chronic pain who have completed cancer treatment, are in clinical remission, and are under cancer surveillance only. The guideline is not intended to apply to patients in treatment for active cancer. The guideline is not intended for patients undergoing active cancer treatment, palliative care, or end-of-life care because of the unique therapeutic goals, ethical considerations, opportunities for medical supervision, and balance of risks and benefits with opioid therapy in such care. The recommendations address the use of opioid pain medication in certain special populations (e.g., older adults and pregnant women) and in populations with conditions posing special risks (e.g., a history of substance use disorder).

The recommendations are not intended to provide guidance on use of opioids as part of medication-assisted treatment for opioid use disorder. 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 this guideline. Readers are referred to other sources for prescribing recommendations within acute care settings and in dental practice, such as the American College of Emergency Physicians' guideline for prescribing of opioids in the emergency department (*31*); the American Society of Anesthesiologists' guideline for acute pain management in the perioperative setting

DRAFT

(*32*); the Washington Agency Medical Directors' Group Interagency Guideline on Prescribing Opioids for Pain, Part II: Prescribing Opioids in the Acute and Subacute Phase (*26*); and the Pennsylvania Guidelines on the Use of Opioids in Dental Practice (*33*). In addition, given the challenges of managing the painful complications of sickle cell disease, readers are referred to the NIH National Heart, Lung, and Blood Institute's Evidence Based Management of Sickle Cell Disease Expert Panel Report for management of sickle cell disease (*34*).

Guideline Development Methods

Guideline Development Using the Grading of Recommendations Assessment, Development, and Evaluation Method

CDC developed this guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (http://www.gradeworkinggroup.org/). This method specifies the systematic review of scientific evidence and offers a transparent approach to grading quality of evidence and strength of recommendations. The method has been adopted and translated by the CDC Advisory Committee for Immunization Practices (ACIP) (*35*). CDC has applied the ACIP translation of the GRADE framework in this guideline. Within the ACIP GRADE framework, the body of evidence is categorized in a hierarchy. This hierarchy reflects degree of confidence in the effect of a clinical action on health outcomes. The categories include type 1 evidence (randomized controlled trials or overwhelming evidence from observational studies), type 2 evidence (randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies), type 3 evidence (observational studies or randomized controlled trials with notable limitations), and type 4 evidence (clinical experience and observations, observational studies with important limitations, or randomized controlled trials with several major limitations). Type of evidence is categorized by study design as well as limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, the magnitude of treatment effects, dose-response gradient, and a constellation of plausible biases that could change observations of effects. Type 1 evidence indicates that one can be very confident that the true effect lies close to that of the estimate of the effect; type 2 evidence means that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; type 3 evidence means that confidence in the effect estimate is limited and the true effect might be substantially different from the estimate of the effect; and type 4 evidence indicates that one has very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of the effect (*35*,*36*). When no studies are present, evidence is considered to be insufficient. The ACIP GRADE framework constructs recommendations in two categories, Category A and Category B. Four major factors determine the category of the recommendation: the quality of evidence, the balance between desirable and undesirable effects, values and preferences, and resource allocation (cost). Category A recommendations apply to all persons in a specified group and indicate that most patients should receive the recommended course of action. Category B recommendations indicate that there should be individual decision making; different choices will be appropriate for different patients, so providers must help patients arrive at a decision consistent with patient values and preferences, and specific clinical situations (*35*). According to the GRADE methodology, a particular quality of evidence does not necessarily imply a particular strength of recommendation (*36*–*38*). Category A recommendations can be made based on type 3 or type 4 evidence when the advantages of a clinical action greatly outweigh the disadvantages based on a consideration of benefits and harms, values and preferences, and costs. Category B recommendations are made when the advantages and disadvantages of a clinical action are more balanced. GRADE methodology is discussed extensively elsewhere (*35*,*37*,*39*).

A previously published 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 (*10*,*40*)

DRAFT

initially served to directly inform the recommendation statements. This systematic clinical evidence review addressed the effectiveness of long-term opioid therapy for outcomes related to pain, function, and quality of life; the comparative effectiveness of different methods for initiating and titrating opioids; the harms and adverse events associated with opioids; and the accuracy of risk-prediction instruments and effectiveness of risk mitigation strategies on outcomes related to overdose, addiction, abuse, or misuse. For the current guideline development, CDC conducted additional literature searches to update the evidence review to include more recently available publications and to answer an additional clinical question about the effect of opioid therapy for acute pain on long-term use (See Online Appendix 1: Clinical Evidence Review, available in the "Supporting Documents" section of the docket). CDC developed GRADE evidence tables to illustrate the quality of the evidence for each clinical question.

As identified in the AHRQ-sponsored clinical evidence review, the overall evidence base for the effectiveness and risks of long-term opioid therapy is low in quality per the GRADE criteria. Thus, contextual evidence that provides information about alternatives to long-term opioid therapy and the epidemiology of opioid pain medication overdose is critical for informing the recommendations. Further, as elucidated by the GRADE Working Group, supplemental information on provider and patient values and preferences and resource allocation can inform judgments of benefits and harms and be helpful for translating the evidence into recommendations. CDC conducted a contextual evidence review to supplement the clinical evidence review based on systematic searches of the literature. The review focused on the following four areas: effectiveness of alternative treatments (i.e., nonpharmacologic and nonopioid pharmacologic treatments); benefits and harms related to opioid therapy (found in epidemiology rather than the clinical randomized trial literature related to specific opioid pain medications, high-dose opioid therapy, co-prescription of opioids with other controlled substances, duration of opioid use, special populations, risk stratification/mitigation approaches, and effectiveness of treatments for addressing potential harms of opioid therapy); provider and patient values and preferences; and resource allocation. CDC constructed narrative summaries of this contextual evidence and used the information to support the clinical recommendations (See Contextual Evidence Review, available in the "Supporting Documents" section of the docket).

On the basis of a review of the clinical and contextual evidence (review methods described in more detail in subsequent sections), CDC drafted recommendation statements focused on 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. CDC then solicited expert opinion in the form of individual ratings, discussions, and written comment to help refine the recommendations.

Solicitation of Expert Opinion

CDC invited a core group of experts (the Core Expert Group [CEG]) to assist in reviewing the evidence and providing perspective on how CDC translated the evidence into draft recommendations. Experts provided individual consultation. The group was composed of subject matter experts, representatives of primary care professional societies and state agencies, and an expert in guideline development methodology.* CDC identified subject matter experts with high scientific standing; appropriate academic and clinical training and relevant clinical experience; and proven scientific excellence in opioid prescribing, addiction, substance use disorder treatment, and pain management. CDC identified representatives from leading primary care professional organizations to represent the audience for this guideline. Finally, CDC identified state agency officials and representatives based on their experience with state guidelines for opioid prescribing that were developed with multiple agency stakeholders and informed by scientific literature and existing evidence-based guidelines.

DRAFT

Prior to their participation, CDC asked potential experts to reveal possible conflicts of interest such as financial relationships with industry, intellectual preconceptions, or previously stated public positions. Experts could not serve if they held conflicts that could be anticipated to have a direct and predictable effect on the recommendations. CDC excluded experts if there was a financial or promotional relationship with a company that makes a product that might be affected by the guideline. CDC reviewed potential nonfinancial conflicts carefully (e.g., intellectual property, travel, public statements or positions such as congressional testimony) to determine if the activities would have a direct and predictable effect on the recommendations. CDC determined the risk of these types of activities to be minimal for the identified experts. All experts completed a statement certifying that there was no potential or actual conflict of interest. Activities that did not pose a conflict (e.g., participation in Food and Drug Administration [FDA] activities or other guideline efforts) are disclosed.
The experts reviewed written summaries of the scientific evidence (both the clinical and contextual evidence reviews conducted for this guideline) and CDC's draft recommendation statements. Experts provided individual ratings for each draft recommendation statement based on the balance of benefits and harms, evidence strength, certainty of values and preferences, cost, recommendation strength, rationale, importance, clarity, and ease of implementation. CDC convened experts at an in-person meeting June 23–24, 2015, in Atlanta, Georgia, to seek the individual views of the experts on the evidence and draft recommendations. The experts provided their individual opinions at the meeting. Experts did not vote on the recommendations or seek to come to a consensus on the recommendations to be included in the guideline; decisions about recommendations to be included in the guideline were made by CDC. At the meeting, CDC noted experts' comments and any dissenting opinions on the recommendations. After revising the guideline, CDC sent it to the experts for review and asked for individual written comments; CDC reviewed these written comments and considered them when making further revisions to the guideline. Experts did not review the latest version of the guideline, or provide approval for the recommendations provided within.

Federal Partner Engagement

Given the scope of this guideline and the interest of agencies across the federal government in appropriate pain management, opioid prescribing, and related outcomes, CDC invited its National Institute of Occupational Safety and Health and CDC's federal partners to observe the expert meeting and provide written comments on the full guideline after the meeting; CDC reviewed comments and incorporated suggestions. Interagency collaboration will be critical for translating these recommendations into clinical practice. Federal partners included representatives from the Substance Abuse and Mental Health Services Administration, the National Institute on Drug Abuse, FDA, the U.S. Department of Veterans Affairs, the U.S. Department of Defense, the Office of the National Coordinator for Health Information Technology, the Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, AHRQ, and the Office of National Drug Control Policy.

Stakeholder Comment

Given the importance of the guideline for a wide variety of stakeholders, CDC designated a Stakeholder Review Group (SRG) to provide comment so that CDC could consider modifications that would improve the recommendations' specificity, applicability, and ease of implementation. The SRG included representatives from professional organizations that represent specialties that commonly prescribe opioids (e.g., pain medicine, physical medicine and rehabilitation), delivery systems within which opioid prescribing occurs (e.g., hospitals), and representation from community organizations with interests in pain management and opioid prescribing.* CDC identified representatives from each of the SRG organizations and provided a copy of the guideline for comment. Once input was received from the full SRG, CDC reviewed all comments individually and carefully considered them when revising the guideline.

DRAFT

Peer Review

Peer review requirements applied to this guideline because it provides influential scientific information that could have a clear and substantial impact on public- and private-sector decisions. Three experts independently reviewed the guideline to determine the reasonableness of recommendations and ensure that scientific uncertainties were clearly identified.* CDC selected peer reviewers based on expertise, diversity of scientific viewpoints, and independence from the guideline development process. CDC assessed and managed potential conflicts of interest using a similar process to that used with the CEG members. No financial interests were identified in the disclosure and review process, and nonfinancial activities were determined to be of minimal risk; thus, no significant conflict of interest concerns were identified. CDC placed the names of peer reviewers on the CDC and the National Center for Injury Prevention and Control Peer Review Agenda websites that are used to provide information about the peer review of influential documents. CDC reviewed peer review comments and revised the guideline.

Constituent Engagement

To obtain perspectives from constituents, including providers and prospective patients, CDC convened a constituent engagement webinar and circulated information about the webinar in advance through announcements to partners. CDC hosted the webinar on September 16 and 17, 2015, provided information about the methodology for developing the guideline, and presented the key recommendations. A fact sheet was posted on the CDC Injury Center website summarizing the guideline development process and clinical practice areas addressed in the guideline; instructions were included on how to submit comments via email. CDC received comments during and for 2 days following the webinar. Comments were reviewed individually and carefully considered when revising the guideline.

Clinical Evidence Review

Primary Clinical Questions

For this guideline, CDC addressed five primary clinical questions regarding the effectiveness, benefits, and harms of long-term opioid therapy for chronic pain through systematic reviews of the scientific evidence. Long-term opioid therapy is defined as use of opioids on most days for >3 months. A previously published AHRQ-funded systematic review on the effectiveness and risks of long-term opioid therapy for chronic pain comprehensively addressed four clinical questions (*10*,*40*). CDC, with the assistance of a methodology expert, searched the literature to identify newly published studies on these four original questions. CDC subsequently developed a fifth clinical question (last in the series below), and in collaboration with a methodologist conducted a systematic review of the scientific evidence to address it. In brief, five clinical questions were addressed:

- The effectiveness of long-term opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for long term (>1 year) outcomes related to pain, function, and quality of life, and how effectiveness varies according to the type/cause of pain, patient demographics, and patient comorbidities (Key Question 1; KQ1).
- The risks of opioids versus placebo or no opioids on abuse, addiction, overdose, and other harms, and how harms vary according to the type/cause of pain, patient demographics, patient comorbidities, and dose (KQ2).
- The comparative effectiveness of opioid dosing strategies (different methods for initiating and titrating opioids; immediate-release versus ER/LA opioids; different ER/LA opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled, continuous versus as-needed dosing; dose escalation versus dose maintenance; opioid rotation versus maintenance; different strategies for treating acute exacerbations of chronic pain; decreasing opioid doses or tapering off versus continuation; and different tapering protocols and strategies) (KQ3).

DRAFT

- The accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse; the effectiveness of risk mitigation strategies (use of risk prediction instruments); effectiveness of risk mitigation strategies including opioid management plans, patient education, urine drug testing, prescription drug monitoring program (PDMP) data, monitoring instruments, monitoring intervals, pill counts, and abuse-deterrent formulations for reducing risk for opioid overdose, addiction, abuse, or misuse; and the comparative effectiveness of treatment strategies for managing patients with addiction (KQ4).
- The effects of prescribing opioid therapy versus not prescribing opioid therapy for acute pain on long-term use (KQ5).

The review was focused on the effectiveness of long-term opioid therapy on long-term (>1 year) outcomes related to pain, function, and quality of life to ensure that findings are relevant to patients with chronic pain and long-term opioid prescribing. 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. A detailed listing of the key questions can be found in Online Appendix 1: Clinical Evidence Review, available in the "Supporting Documents" section of the docket.

Clinical Evidence Systematic Review Methods

Complete methods and data for the 2014 AHRQ report, upon which this updated systematic review is based, have been published previously (*10*,*40*). Study authors developed the protocol using a standardized process (*41*) with input from experts and constituents and registered the protocol in the PROSPERO database (*42*). CDC conducted an updated literature search using the same search strategies as in the original review. Seven additional studies met inclusion criteria and were added to the review. Information about data sources and searches, study selection, data extraction and quality assessment, data synthesis, and update search yield and new evidence for the current review can be found in Online Appendix 1: Clinical Evidence Review, available in the "Supporting Documents" section of the docket.

Summary of Findings for Clinical Questions

The main findings of this updated review are consistent with the findings of the 2014 AHRQ report (*10*). In summary, 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, though evidence suggests risk for serious harms that appears to be dose-dependent. These findings supplement findings from a previous review of the effectiveness of opioids for adults with chronic noncancer pain. In this previous review, based on randomized trials predominantly <12 weeks in duration, opioids were found to be moderately effective for pain relief, with small benefits for functional outcomes; although estimates vary, based on uncontrolled studies, a high percentage of patients discontinued long-term opioid use because of lack of efficacy and because of adverse events (*24*).

The GRADE evidence summary with type of evidence ratings for the five clinical questions for the current evidence review are outlined (Table). This summary is based on studies included in the AHRQ 2014 review (35 studies) plus additional studies identified in the updated search (7 studies). Additional details on findings from the original review are available in the full 2014 AHRQ report (*10*,*40*). Full details on the clinical evidence review findings supporting this guideline can be found in Online Appendix 1: Clinical Evidence Review, available in the "Supporting Documents" section of the docket.

Effectiveness

For KQ1, no study of opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for chronic pain evaluated long-term (>1 year) outcomes related to pain, function, or quality of life. Most placebo-

controlled randomized trials were ≤6 weeks in duration. Thus, the body of evidence for KQ1 is rated as insufficient (0 studies contributing) (*10*).

Harms

For KQ2, the body of evidence is rated as type 3 (12 studies contributing; 11 from the original review plus 1 new study). One fair-quality cohort study found that long-term opioid therapy is associated with increased risk for an opioid abuse or dependence diagnosis versus no opioid prescription (*18*). Rates of opioid abuse or dependence ranged from 0.7% with lower-dose (≤36 MME) chronic therapy to 6.1% with higher-dose (≥120 MME) chronic therapy, versus 0.004% with no opioids. Ten fair-quality uncontrolled studies reported estimates of opioid abuse, addiction, and related outcomes (*43–53*). In primary care settings, prevalence of opioid dependence (using DSM-IV criteria) ranged from 3% to 26% (*43*,*44*,*47*). In pain clinic settings, prevalence of addiction ranged from 2% to 14% (*45*,*46*,*48*,*49*,*51–53*).

Factors associated with increased risk for misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications (*44*,*50*). Two studies reported on the association between opioid use and risk for overdose (*54*,*55*). One large fair-quality retrospective cohort study found that recent opioid use was associated with increased risk for any overdose events and serious overdose events versus nonuse (*54*). It also found higher doses associated with increased risk. Relative to 1–19 MME/day, the adjusted hazard ratio (HR) for any overdose event (consisting of mostly nonfatal overdose) was 1.44 for 20 to 49 MME/day, 3.73 for 50–99 MME/day, and 8.87 for ≥100 MME/day. A similar pattern was observed for serious overdose. A good-quality population-based, nested case-control study also found a dose-dependent association with risk for overdose death (*55*). Relative to 1–19 MME/day, the adjusted odds ratio (OR) was 1.32 for 20–49 MME/day, 1.92 for 50–99 MME/day, 2.04 for 100–199 MME/day, and 2.88 for ≥200 MME/day.

Findings of increased fracture risk for current opioid use, versus nonuse, were mixed in two studies (*56*,*57*). Two studies found an association between opioid use and increased risk for cardiovascular events (*58*,*59*). Indirect evidence was found for endocrinologic harms (increased use of medications for erectile dysfunction or testosterone from one previously included study; laboratory-defined androgen deficiency from one newly reviewed study) (*60*,*61*). One study found that opioid dosages ≥20 MME/day were associated with increased odds of road trauma among drivers (*62*).

Opioid Dosing Strategies

For KQ3, the body of evidence is rated as type 4 (14 studies contributing; 12 from the original review plus two new studies). For initiation and titration of opioids, the 2014 AHRQ report found insufficient evidence from three fair-quality, open-label trials to determine comparative effectiveness of ER/LA versus immediate-release opioids for titrating patients to stable pain control (*63*,*64*). One new fair-quality cohort study of Veterans Affairs patients found initiation of therapy with an ER/LA opioid associated with greater risk for nonfatal overdose than initiation with an immediate-release opioid, with risk greatest in the first 2 weeks after initiation of treatment (*65*).

For comparative effectiveness and harms of ER/LA opioids, the 2014 AHRQ report included three randomized, head-to-head trials of various ER/LA opioids that found no clear differences in 1-year outcomes related to pain or function (*66–68*) but had methodological shortcomings. A fair-quality retrospective cohort study based on national Veterans Health Administration system pharmacy data found that methadone was associated with lower overall risk for all-cause mortality versus morphine (*69*), and a fair-quality retrospective cohort study based on Oregon Medicaid data found no statistically significant differences between methadone and long-acting morphine in risk for death or overdose symptoms (*70*). However, a new observational study (*71*) found methadone associated with increased risk for overdose versus sustained-release morphine among Tennessee Medicaid patients. The observed inconsistency in study findings suggests that risks of methadone might vary in different settings as a

function of different monitoring and management protocols, though more research is needed to understand factors associated with safer methadone prescribing.

For dose escalation, the 2014 AHRQ report included one fair-quality randomized trial that found no differences between more liberal dose escalation and maintenance of current doses after 12 months in pain, function, all-cause withdrawals, or withdrawals due to opioid misuse (*72*). However, the difference in opioid dosages prescribed at the end of the trial was relatively small (mean 52 MME/day with more liberal dosing versus 40 MME/day). Evidence on other comparisons related to opioid dosing strategies (ER/LA versus immediate-release opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled continuous dosing versus as-needed dosing; or opioid rotation versus maintenance of current therapy; long-term effects of strategies for treating acute exacerbations of chronic pain) was not available or too limited to determine effects on long-term clinical outcomes. For example, evidence on the comparative effectiveness of opioid tapering or discontinuation versus maintenance, and of different opioid tapering strategies, was limited to small, poor-quality studies (*73–75*).

Risk Assessment and Mitigation

For KQ4, the body of evidence is rated as type 3 for the accuracy of risk assessment tools and insufficient for the effectiveness of use of risk assessment tools and mitigation strategies in reducing harms (six studies contributing; four from the original review plus two new studies). The 2014 AHRQ report included four studies (76–79) on the accuracy of risk assessment instruments, administered prior to opioid therapy initiation, for predicting opioid abuse or misuse. Results for the Opioid Risk Tool (ORT) (77–79) were extremely inconsistent; evidence for other risk assessment instruments was very sparse, and studies had serious methodological shortcomings. One additional fair-quality (80) and one poor-quality (81) study identified for this update compared the predictive accuracy of the ORT, the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), and the Brief Risk Interview. For the ORT, sensitivity was 0.58 and 0.75 and specificity 0.54 and 0.86; for the SOAPP-R, sensitivity was 0.53 and 0.25 and specificity 0.62 and 0.73; and for the Brief Risk Interview, sensitivity was 0.73 and 0.83 and specificity 0.43 and 0.88. For the ORT, positive likelihood ratios ranged from noninformative (positive likelihood ratio close to 1) to moderately useful (positive likelihood ratio >5). The SOAPP-R was associated with noninformative likelihood ratios (estimates close to 1) in both studies.

No study evaluated the effectiveness of risk mitigation strategies (use of risk assessment instruments, opioid management plans, patient education, urine drug testing, use of PDMP data, use of monitoring instruments, more frequent monitoring intervals, pill counts, or use of abuse-deterrent formulations) for improving outcomes related to overdose, addiction, abuse, or misuse.

Effects of Opioid Therapy for Acute Pain on Long-Term Use

For KQ5, the body of evidence is rated as type 3 (two new studies contributing). Two fair-quality retrospective cohort studies found opioid therapy prescribed for acute pain associated with greater likelihood of long-term use. One study evaluated opioid-naïve patients who had undergone low-risk surgery, such as cataract surgery and varicose vein stripping (82). Use of opioids within 7 days of surgery was associated with increased risk for use at 1 year. The other study found that among patients with a workers' compensation claim for acute low back pain, compared to patients who did not receive opioids early after injury (defined as use within 15 days following onset of pain), patients who did receive early opioids had an increased likelihood of receiving five or more opioid prescriptions 30 to 730 days following onset that increased with greater early exposure (83).

DRAFT

Contextual Evidence Review

Primary Areas of Focus

Contextual evidence is complementary information that assists in translating the clinical research findings into recommendations. CDC conducted contextual evidence reviews on four topics to supplement the clinical evidence review findings:

- Effectiveness of alternative treatments, including nonpharmacologic (e.g., cognitive behavioral therapy [CBT], exercise therapy, interventional treatments, and multimodal pain treatment) and nonopioid pharmacologic treatments (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], antidepressants, and anticonvulsants), including studies of any duration.
- Benefits and harms of opioid therapy, including findings from the epidemiology and public health literature (rather than the clinical trial literature included in the clinical evidence review) related to specific opioids, high-dose therapy, co-prescription with other controlled substances, duration of use, special populations, and potential usefulness of risk stratification/mitigation approaches, in addition to effectiveness of treatments associated with addressing potential harms of opioid therapy (opioid use disorder).
- Provider 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.

CDC also reviewed clinical guidelines that were relevant to opioid prescribing and could inform or complement the CDC recommendations under development (e.g., guidelines on alternative treatments and guidelines with recommendations related to specific provider actions such as urine drug testing or opioid tapering protocols).

Contextual Evidence Review Methods

Given the public health urgency for developing opioid prescribing recommendations, a rapid review was required for the contextual evidence review for the current guideline. Rapid reviews are used when there is a need to streamline the systematic review process to obtain evidence quickly (*84*). Methods used to streamline the process include limiting searches by databases, years, and languages considered, and truncating quality assessment and data abstraction protocols. CDC conducted "rapid reviews" of the contextual evidence on alternative treatments, benefits and harms, values and preferences, and resource allocation.

Detailed information about contextual evidence data sources and searches, inclusion criteria, study selection, and data extraction and synthesis are available in Online Appendix 2: Contextual Evidence Review, available in the "Supporting Documents" section of the docket. In brief, CDC conducted systematic literature searches to identify original studies, systematic reviews, and clinical guidelines, depending on the topic being searched. CDC also solicited publication referrals from subject matter experts. Given the need for a rapid review process, grey literature (e.g., literature by academia, organizations, or government in the forms of reports, documents, or proceedings not published by commercial publishers) was not systematically searched. Database sources, including MEDLINE, PsycINFO, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, varied by topic. Multiple reviewers scanned study abstracts identified through the database searches and extracted relevant studies for review. CDC constructed narrative summaries and tables based on relevant articles that met inclusion criteria (see Online Appendix 2 for criteria).

DRAFT

Findings from the contextual reviews provide indirect evidence and should be interpreted accordingly. CDC did not formally rate the quality of evidence for the studies included in the contextual evidence review using the GRADE method. The studies that addressed benefits and harms, values and preferences, and resource allocation most often employed observational methods, used short follow-up periods, and evaluated selected samples. Therefore the strength of the evidence from these contextual review areas was considered to be low, comparable to type 3 or type 4 evidence. The quality of evidence for nonopioid pharmacologic and nonpharmacologic pain treatments was generally rated as moderate, comparable to type 2 evidence, in systematic reviews and clinical guidelines (e.g., for treatment of chronic neuropathic pain, low back pain, osteoarthritis, and fibromyalgia). Similarly, the quality of evidence on pharmacologic and psychosocial opioid use disorder treatment was generally rated as moderate, comparable to type 2 evidence, in systematic reviews and clinical guidelines.

Summary of Findings for Contextual Areas

Full narrative reviews and tables that summarize key findings from the contextual evidence review are provided in Online Appendix 2: Contextual Evidence Review, available in the "Supporting Documents" section of the docket.

Effectiveness of Alternative Treatments

Several nonpharmacologic and nonopioid pharmacologic treatments have been shown to be effective in managing chronic pain in studies ranging in duration from 2 weeks to 6 months. For example, CBT that trains patients in behavioral techniques and helps patients modify situational factors and cognitive processes that exacerbate pain has small positive effects on disability and catastrophic thinking (*85*). Exercise therapy can help reduce pain and improve function in chronic low back pain (*86*), improve function and reduce pain in osteoarthritis of the knee (*87*) and hip (*88*), and improve well-being, fibromyalgia symptoms, and physical function in fibromyalgia (*89*). Multimodal and multidisciplinary therapies (e.g., therapies that combine exercise and related therapies with psychologically based approaches) can help reduce pain and improve function more effectively than single modalities (*90*,*91*). Nonopioid pharmacologic approaches used for pain include analgesics such as acetaminophen, NSAIDs, and cyclooxygenase 2 (COX-2) inhibitors; selected anticonvulsants; and selected antidepressants (particularly tricyclics and serotonin and norepinephrine reuptake inhibitors [SNRIs]). Multiple guidelines recommend acetaminophen as first-line pharmacotherapy for osteoarthritis (*92–97*) or for low back pain (*98*) but note that it should be avoided in liver failure and that dosage should be reduced in patients with hepatic insufficiency or a history of alcohol abuse (*97*). Although guidelines also recommend NSAIDs as first-line treatment for osteoarthritis or low back pain (*94*,*98*), NSAIDs and COX-2 inhibitors do have risks, including gastrointestinal bleeding or perforation as well as renal and cardiovascular risks (*99*). FDA has recently strengthened existing label warnings that NSAIDs increase risks for heart attack and stroke, including that these risks might increase with longer use or at higher doses (*100*). Several guidelines agree that first- and second-line drugs for neuropathic pain include anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, and SNRIs (*101–104*). Interventional approaches such as epidural injection for certain conditions (e.g., lumbar radiculopathy) can provide short-term improvement in pain and in function that can facilitate exercise therapy (*105–107*). However, evidence has not demonstrated long-term benefit, and epidural injection has been associated with rare but serious adverse events, including loss of vision, stroke, paralysis, and death (*108*).

Benefits and Harms of Opioid Therapy

Balance between benefits and harms is a critical factor influencing the strength of clinical recommendations. In particular, CDC considered what is known from the epidemiology research about benefits and harms related to specific opioids and formulations, high dose therapy, co-prescription with

other controlled substances, duration of use, special populations, and risk stratification and mitigation approaches. Additional information on benefits and harms of long-term opioid therapy from studies meeting rigorous selection criteria can be found in the clinical evidence review (e.g., see KQ2). CDC also considered the number of persons experiencing chronic pain, numbers potentially benefiting from opioids, and numbers affected by opioid-related harms. A review of these data is presented in the background section of this document, with detailed information presented available in Online Appendix 2: Contextual Evidence Review, available in the "Supporting Documents" section of the docket. Finally, CDC considered the effectiveness of treatments that addressed potential harms of opioid therapy (opioid use disorder).

Regarding specific opioids and formulations, as noted by FDA, there are serious risks of ER/LA opioids, and the indication for this class of medications is for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment in patients for whom alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain (*109*). Time-scheduled opioid use was associated with substantially higher average daily opioid dosage than as-needed opioid use in one study (*110*). Methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for pain. Methadone has been found to account for as much as a third of opioid-related overdose deaths involving single or multiple drugs in states that participated in the Drug Abuse Warning Network, which was more than any opioid other than oxycodone, despite representing <2% of opioid prescriptions outside of opioid treatment programs in the United States; further, methadone was involved in twice as many single-drug deaths as any other prescription opioid (*111*).

Regarding high-dose therapy, several epidemiologic studies that were excluded from the clinical evidence review because patient samples were not restricted to patients with chronic pain also examined the association between opioid dosage and overdose risk (*19,20,112–114*). Consistent with the clinical evidence review, the contextual review found that opioid-related overdose risk is dose-dependent, with higher opioid dosages associated with increased overdose risk. Two of these studies (*19,20*), as well as the two studies in the clinical evidence review (*115,116*), evaluated similar MME/day dose ranges for association with overdose risk. In these four studies, compared with opioids prescribed at <20 MME/day, the odds of overdose among patients prescribed opioids for chronic nonmalignant pain were between 1.3 (*116*) and 1.9 (*20*) for dosages of 20 to <50 MME/day, between 1.9 (*116*) and 4.6 (*20*) for dosages of 50 to <100 MME/day, and between 2.0 (*116*) and 8.9 (*115*) for dosages of ≥100 MME/day. A recent study of Veterans Health Administration patients with chronic pain found that patients who died of overdoses related to opioids were prescribed higher opioid dosages (mean: 98 MME/day; median: 60 MME/day) than controls (mean: 48 MME/day, median: 25 MME/day) (Amy Bohnert, unpublished data, 2015). Finally, another recent study of overdose deaths among state residents with and without opioid prescriptions revealed that prescription opioid-related overdose mortality rates rose rapidly up to prescribed doses of 200 MME/day, after which the mortality rates continued to increase but grew more gradually (*117*).

Regarding co-prescription of opioids with benzodiazepines, epidemiologic studies suggest that concurrent use of benzodiazepines and opioids might put patients at greater risk for potentially fatal overdose. Three studies of fatal overdose deaths found evidence of concurrent benzodiazepine use in 31%–61% of decedents (*116–118*). In one of these studies (*118*), among decedents who received an opioid prescription, those whose deaths were related to opioids were more likely to have obtained opioids from multiple physicians and pharmacies than decedents whose deaths were not related to opioids.

DRAFT

Regarding duration of use, patients can experience tolerance and loss of effectiveness of opioids over time (*119*). Patients who do not experience clinically meaningful pain relief early in treatment (i.e., within 1 month) are unlikely to experience pain relief with longer-term use (*120*).

Regarding populations potentially at greater risk for harm, risk is greater for patients with sleep apnea or other causes of sleep-disordered breathing, patients with renal or hepatic insufficiency, older adults, pregnant women, patients with depression or other mental health conditions, and patients with alcohol or other substance use disorders. Interpretation of clinical data on the effects of opioids on sleep-disordered breathing is difficult because of the types of study designs and methods employed, and there is no clear consensus regarding association with risk for developing obstructive sleep apnea syndrome (*121*). However, opioid therapy can decrease respiratory drive, a high percentage of patients on long-term opioid therapy have been reported to have an abnormal apnea-hypopnea index (*122*), opioid therapy can worsen central sleep apnea in obstructive sleep apnea patients, and it can cause further desaturation in obstructive sleep apnea patients not on continuous positive airway pressure (CPAP) (*25*). Reduced renal or hepatic function can result in greater peak effect and longer duration of action and reduce the dose at which respiratory depression and overdose occurs (*123*). Age-related changes in patients aged ≥65 years, such as reduced renal function and medication clearance, even in the absence of renal disease (*124*), result in a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose. Older adults might also be at increased risk for falls and fractures related to opioids (*125–127*). Opioids used in pregnancy can be associated with additional risks to both mother and fetus. Opioid treatment during pregnancy has been found to be associated with birth defects, including neural tube defects (*128,129*), congenital heart defects (*129*), and gastroschisis (*129*); preterm delivery (*130*), poor fetal growth (*130*), stillbirth (*130*), and neonatal opioid withdrawal syndrome (*131*). Patients with mental health comorbidities and patients with histories of substance use disorders might be at higher risk than other patients for opioid use disorder (*132–134*). Recent analyses found that depressed patients were at higher risk for drug overdose than patients without depression, particularly at higher opioid dosages, although investigators were unable to distinguish unintentional overdose from suicide attempts (*135*). In case-control and case-cohort studies, substance abuse/dependence was more prevalent among patients experiencing overdose than among patients not experiencing overdose (12% versus 6% [*115*], 40% versus 10% [*20*], and 26% versus 9% [*19*]).

Regarding risk stratification approaches, limited evidence was found regarding benefits and harms. Potential benefits of PDMPs and urine drug testing include the ability to identify patients who might be at higher risk for opioid overdose or opioid use disorder, and help determine which patients will benefit from greater caution and increased monitoring or interventions when risk factors are present. For example, one study found that most fatal overdoses could be retrospectively identified based on two pieces of information (multiple prescribers and high total daily opioid dosage, both important risk factors for overdose [*112,136*]) that are available to prescribers in the PDMP (*112*). However, limited evaluation of PDMPs at the state level has revealed mixed effects on changes in prescribing and mortality outcomes (*23*). Potential harms of risk stratification include underestimation of risks of opioid therapy when screening tools are not adequately sensitive, as well as potential overestimation of risk, which could lead to inappropriate clinical decisions.

Regarding risk mitigation approaches, limited evidence was found regarding benefits and harms. Although no studies were found to examine prescribing of naloxone with opioid pain medication in primary care settings, naloxone distribution through community-based programs providing prevention services for substance users has been demonstrated to be associated with decreased risk for opioid overdose death at the community level (*137*).

Concerns have been raised that prescribing changes such as dose reduction might be associated with unintended negative consequences, such as patients seeking heroin or other illicitly obtained opioids

(*138*) or interference with appropriate pain treatment (*139*). With the exception of a study noting an association between an abuse-deterrent formulation of OxyContin and heroin use, showing that some patients in qualitative interviews reported switching to another opioid, including heroin, for many reasons, including cost and availability as well as ease of use (*140*), CDC did not identify studies evaluating these potential outcomes.

Finally, regarding the effectiveness of opioid use disorder treatments, methadone and buprenorphine for opioid dependence have been found to increase retention in treatment and to decrease illicit opioid use among patients with opioid dependence involving heroin, particularly when psychosocial treatments (e.g., contingency management, community reinforcement, psychotherapeutic counseling, and family therapy) are used in conjunction with medication-assisted therapy (*141–144*).

Provider and Patient Values and Preferences

Provider and patient values and preferences can inform how benefits and harms of long-term opioid therapy are weighted and estimate the effort and resources required to effectively provide implementation support. Many physicians lack confidence in their ability to prescribe opioids safely (*145*), to predict (*146*) or detect (*147*) prescription drug abuse, and to discuss abuse with their patients (*147*). Although providers have reported favorable beliefs and attitudes about improvements in pain and quality of life attributed to opioids (*148*), most consider prescription drug abuse to be a "moderate" or "big" problem in their community, and large proportions are "very" concerned about opioid addiction (55%) and death (48%) (*149*). Majorities of providers have reported adverse events including tolerance (62%) and physical dependence (56%) occurring often among patients (*149*). Providers do not consistently use practices intended to decrease the risk for misuse, such as PDMPs (*150,151*), urine drug testing (*152*), and opioid treatment agreements (*153*). This is likely due in part to challenges related to registering for PDMP access and logging into the PDMP (which can interrupt normal clinical workflow if data are not integrated into electronic health record systems) (*154*), competing clinical demands, perceived inadequate time to discuss the rationale for urine drug testing and to order confirmatory testing, and feeling unprepared to interpret and address results (*155*).

Many patients do not have an opinion about "opioids" or know what this term means (*156*). Most are familiar with the term "narcotics." About a third associated "narcotics" with addiction or abuse, and about half feared "addiction" from long-term "narcotic" use (*156*). Most patients taking opioids experience side effects (73% of patients taking hydrocodone for noncancer pain [*157*], 96% of patients taking opioids for chronic pain [*158*]), and side effects, rather than pain relief, have been found to explain most of the variation in patients' preferences related to taking opioids (*158*). For example, patients taking hydrocodone for noncancer pain commonly reported side effects including dizziness, headache, fatigue, drowsiness, nausea, vomiting, and constipation (*157*). Patients with chronic pain in focus groups emphasized effectiveness of goal setting for increasing motivation and functioning (*159*). Patients taking high dosages report reliance on opioids despite ambivalence about their benefits (*160*) and regardless of pain reduction, reported problems, concerns, side effects, or perceived helpfulness (*161*).

Resource Allocation

Resource allocation (cost) is an important consideration in understanding the feasibility of clinical recommendations. CDC searched for evidence on opioid therapy compared with alternative treatments; costs of misuse, abuse, and overdose from prescription opioids; and costs of specific risk mitigation strategies (e.g., urine drug testing). Yearly direct and indirect costs related to prescription opioids have been estimated (based on studies published since 2010) to be $53.4 billion for nonmedical use of prescription opioids (*162*); $55.7 billion for abuse, dependence, and misuse of prescription opioids (*163*); and $20.4 billion for direct and indirect costs related to opioid-related overdose alone (*164*). In 2012, total expenses for outpatient prescription opioids were estimated at $9.0 billion, an increase of 120%

DRAFT

from 2002 (*165*). Although there are perceptions that opioid therapy for chronic pain is less expensive than more time-intensive nonpharmacologic management approaches, many pain treatments, including acetaminophen, NSAIDs, tricyclic antidepressants, and massage therapy, are associated with lower mean and median annual costs compared with opioid therapy (*166*). COX-2 inhibitors, SNRIs, anticonvulsants, topical analgesics, physical therapy, and CBT are also associated with lower median annual costs compared with opioid therapy (*166*). Limited information was found on costs of strategies to decrease risks associated with opioid therapy; however, urine drug testing, including screening and confirmatory tests, has been estimated to cost $211–$363 per test (*167*).

Recommendations

The recommendations are grouped into three areas for consideration:

- Determining when to initiate or continue opioids for chronic pain.
- Opioid selection, dosage, duration, follow-up, and discontinuation.
- Assessing risk and addressing harms of opioid use.

There are 12 recommendations (Box 1). Each recommendation is followed by a rationale for the recommendation, with considerations for implementation noted. In accordance with the ACIP GRADE process, CDC based the recommendations on consideration of the clinical evidence, contextual evidence (including benefits and harms, values and preferences, resource allocation), and expert opinion. For each recommendation statement, CDC notes the recommendation category (A or B) and the type of the evidence (1, 2, 3, or 4) supporting the statement (Box 2). Experts from the Core Expert Group ("experts") expressed overall support for all recommendations, as well as for the indicated category of the recommendations. Where differences in expert opinion emerged for detailed actions within the clinical recommendations or for implementation considerations, CDC notes the differences of opinion in the supporting rationale statements.

Category A recommendations indicate that most patients should receive the recommended course of action; category B recommendations indicate that different choices will be appropriate for different patients, requiring providers to help patients arrive at a decision consistent with patient values and preferences and specific clinical situations. Consistent with the ACIP (*35*) and GRADE process (*38*), category A recommendations were made, even with type 3 and 4 evidence, when there was broad agreement that the advantages of a clinical action greatly outweighed the disadvantages based on a consideration of benefits and harms, values and preferences, and resource allocation. Category B recommendations were made when there was broad agreement that the advantages and disadvantages of a clinical action were more balanced, but advantages were significant enough to warrant a recommendation. All recommendations are category A recommendations, with the exception of recommendation 10, which is rated as category B. Recommendations were associated with a range of evidence types, from type 3 to type 4.

In summary, the categorization of recommendations was based on the following assessment:

- No evidence shows a long-term benefit of opioids in pain and function for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized trials $\leq$6 weeks in duration).
- Extensive evidence shows the possible harms of opioids (including abuse and dependence, overdose, myocardial infarction, motor vehicle crashes).
- Extensive evidence suggests benefits of alternative treatments compared with long-term opioid therapy, including nonpharmacologic therapy and nonopioid pharmacologic therapy, with less harm.

DRAFT

Determining When to Initiate or Continue Opioids for Chronic Pain

1. **Nonpharmacologic therapy and nonopioid 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).**

Patients with pain should receive treatment that provides the greatest benefits relative to risks. Although opioids can reduce pain during short-term use, effects appear relatively small. The clinical evidence review found insufficient evidence to determine whether pain relief is sustained and whether function or quality of life improves with long-term opioid therapy (that is, use of opioids on most days for >3 months) (KQ1). Evidence is limited or insufficient for improved pain or function with long-term use of opioids for several chronic pain conditions for which opioids are commonly prescribed, such as low back pain (*168*), headache (*169*), and fibromyalgia (*170*). While benefits for pain relief, function, and quality of life with long-term opioid use for chronic pain are uncertain, risks associated with long-term opioid use are clearer and significant. Based on the clinical evidence review, long-term opioid use for chronic pain is associated with serious risks including increased risk for abuse and dependence, overdose, myocardial infarction, and motor vehicle crashes (KQ2). At a population level, more than 16,000 persons in the United States die every year from opioid pain-medication-related overdoses (contextual evidence review).

Based on contextual evidence, many nonpharmacologic therapies, including physical therapy, weight loss for knee osteoarthritis, complementary and alternative therapies (e.g., manipulation, massage, and acupuncture), psychological therapies such as CBT, and certain interventional procedures can ameliorate chronic pain. In particular, there is high-quality evidence that exercise therapy (a prominent modality in physical therapy) for hip (*88*) or knee (*87*) osteoarthritis reduces pain and improves function immediately after treatment and that the improvements are sustained for at least 2–6 months. Exercise therapy also can help reduce pain and improve function in low back pain and can improve global well-being and physical function in fibromyalgia (*86*,*89*). CBT is an activating therapy that addresses psychosocial contributors to pain and improves function (*85*). Despite this, these therapies are not always or fully covered by insurance, and cost can be a barrier for patients. Multimodal therapies and multidisciplinary biopsychosocial rehabilitation-combining approaches (e.g., psychological therapies with exercise) can reduce long-term pain and disability compared with usual care and compared with physical treatments (e.g., exercise) alone. Multimodal therapies are not always available or reimbursed by insurance and can be time-consuming and costly for patients. Multimodal therapies might therefore be most helpful in patients not responding to single-modality therapy, and combinations should be tailored depending on patient needs, cost, and convenience. Interventional approaches such as arthrocentesis and intraarticular glucocorticoid injection for pain associated with rheumatoid arthritis (*105*) or osteoarthritis (*106*) and subacromial corticosteroid injection for rotator cuff disease (*107*) can provide short-term improvement in pain and function and can facilitate exercise therapy. However, long-term benefit has not been demonstrated, and evidence is insufficient to determine the extent to which repeated injection increases potential risks such as articular cartilage changes (in osteoarthritis) and sepsis (*106*). Epidural injection has been associated with rare but serious adverse events (*108*).

Several nonopioid pharmacologic therapies (including acetaminophen, NSAIDs, and selected antidepressants and anticonvulsants) are effective for chronic pain. In particular, acetaminophen and NSAIDs can be useful for arthritis and low back pain. Selected anticonvulsants such as pregabalin and gabapentin can improve pain in diabetic neuropathy, post-herpetic neuralgia, and fibromyalgia (contextual evidence review). Pregabalin, gabapentin, and carbamazepine are FDA-approved for treatment of certain neuropathic pain conditions, and pregabalin is FDA approved for fibromyalgia management. In patients with or without depression, tricyclic antidepressants and SNRIs provide effective analgesia for neuropathic pain conditions including diabetic neuropathy and post-herpetic

DRAFT

neuralgia, often at lower dosages and with a shorter time to onset of effect than for treatment of depression (see contextual evidence review). Tricyclics and SNRIs can also relieve fibromyalgia symptoms. The SNRI duloxetine is FDA-approved for the treatment of diabetic neuropathy and fibromyalgia. Because patients with chronic pain often suffer from concurrent depression (*133*), and depression can exacerbate physical symptoms including pain (*171*), patients with co-occurring pain and depression are especially likely to benefit from antidepressant medication (see Recommendation 8).

Nonopioid pharmacologic therapies are not generally associated with drug dependence, and the numbers of fatal overdoses associated with nonopioid medications are a fraction of those associated with opioid medications (contextual evidence review). However, nonopioid pharmacologic therapies are associated with risks, particularly in older patients, pregnant patients, and patients with certain co-morbidities such as cardiovascular, renal, gastrointestinal, and liver disease (see contextual evidence review) and should be used only after assessment and determination that expected benefits outweigh these risks.

Given uncertain benefits and substantial risks, experts agreed that opioids should not be considered first-line or routine therapy for chronic pain (i.e., pain continuing or expected to continue longer than 3 months or past the time of normal tissue healing) outside of active cancer, palliative, and end-of-life care. Nonpharmacologic therapy such as exercise therapy and CBT should be used to reduce pain and improve function in patients with chronic pain. Nonopioid pharmacologic therapy should be used when benefits outweigh risks and should be combined with nonpharmacologic therapy to reduce pain and improve function. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate, to provide greater benefits to patients in improving pain and function.

2. **Before starting opioid therapy for chronic pain, 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 if unsuccessful. 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).**

The clinical evidence review found insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and found an increased risk for serious harms related to long-term opioid therapy that appears to be dose-dependent. In addition, studies on currently available risk assessment instruments were sparse and showed inconsistent results (KQ4). The clinical evidence review for the current guideline considered studies with outcomes examined at ≥1 year that compared opioid use versus nonuse or placebo. Studies of opioid therapy for chronic pain that did not have a nonopioid control group have found that although many patients discontinue opioid therapy for chronic noncancer pain due to adverse effects or insufficient pain relief, there is weak evidence that patients who are able to continue opioid therapy for at least 6 months can experience clinically significant pain relief and insufficient evidence that function or quality of life improves (*172*). These findings suggest that it is very difficult for providers to predict whether benefits of opioids for chronic pain will outweigh risks of ongoing treatment for individual patients. Opioid therapy should not be initiated without consideration of an "exit strategy" to be used if the therapy is unsuccessful.

Experts agreed that before opioid therapy is initiated for chronic pain outside of active cancer, palliative, and end-of-life care, providers should determine how effectiveness will be evaluated and should establish treatment goals with patients. Because the line between acute pain and initial chronic pain is not always clear, it might be difficult for providers to determine when they are initiating opioids for chronic pain rather than treating acute pain. Pain lasting longer than 3 months or past the time of normal tissue healing (which could be significantly shorter than 3 months, depending on the condition) is generally no longer considered acute. However, establishing treatment goals with a patient who has already received opioid therapy for 3 months would defer this discussion well past the point of initiation

DRAFT

of opioid therapy for chronic pain. Providers often write prescriptions for long-term use in 30-day increments, and opioid prescriptions written for ≥30 days are likely to represent initiation or continuation of long-term opioid therapy. Prior to writing an opioid prescription for ≥30 days, providers should establish treatment goals with patients. Providers seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy. Although the clinical evidence review did not find studies evaluating the effectiveness of written agreements or treatment plans (KQ4), providers and patients who set a plan in advance will clarify expectations regarding how opioids will be prescribed and monitored, as well as situations in which opioids will be discontinued or doses tapered (e.g., if treatment goals are not met, opioids are no longer needed, or adverse events put the patient at risk) to improve patient safety.

Experts thought that goals should include improvement in both pain relief and function (and therefore in quality of life). However, there are some clinical circumstances under which reductions in pain without improvement in function might be a more realistic goal (e.g., diseases typically associated with progressive functional impairment or catastrophic injuries such as spinal cord trauma). Experts agreed that providers may use validated instruments such as the three-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale (*173*) to track patient outcomes. Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function (*174*). Monitoring progress toward patient-centered functional goals (e.g., walking the dog or walking around the block, returning to part-time work, attending family sports or recreational activities) can also contribute to the assessment of functional improvement. Providers should use these goals in assessing benefits of opioid therapy for individual patients and in weighing benefits against risks of continued opioid therapy (see Recommendation 7, including recommended intervals for follow-up). If patients receiving opioid therapy for chronic pain do not experience meaningful improvements in both pain and function compared with prior to initiation of opioid therapy, providers should consider working with patients to taper and discontinue opioids (see Recommendation 7) and should use nonpharmacologic and nonopioid pharmacologic approaches to pain management (see Recommendation 1).

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).

The clinical evidence review did not find studies evaluating effectiveness of patient education or opioid treatment plans as risk-mitigation strategies (KQ4). However, the contextual evidence review found that many patients lack information about opioids and identified concerns that some providers miss opportunities to effectively communicate about safety (e.g., when unexpected results are found in PDMP information or on urine drug testing). Given the substantial evidence gaps on opioids, uncertain benefits of long-term use, and potential for serious harms, patient education and discussion before starting opioid therapy are critical so that patient preferences and values can be understood and used to inform clinical decisions. Experts agreed that essential elements to communicate to patients before starting and periodically during opioid therapy include realistic expected benefits, common and serious harms, and expectations for provider and patient responsibilities to mitigate risks of opioid therapy.

Providers should involve patients in decisions about whether to start or continue opioid therapy. Given potentially serious risks of long-term opioid therapy, providers should ensure that patients are aware of potential benefits of, harms of, and alternatives to opioids before starting or continuing opioid therapy. Providers should do 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

DRAFT

pain or function with long-term use, and that complete relief of pain is unlikely (clinical evidence review, KQ1).

- 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 overdose and development of a potentially serious lifelong opioid use disorder that can cause distress and inability to fulfill major role obligations.
- Advise patients about common adverse effects of opioids, such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opioids. To prevent constipation associated with opioid use, advise patients to increase hydration and fiber intake and to maintain or increase physical activity. Stool softeners or laxatives might be needed.
- Discuss increased risks for opioid use disorder, overdose, and death at higher dosages, along with the importance of taking only the amount of opioids prescribed, i.e., not taking more opioids or taking them more often.
- Review increased risks for overdose when opioids are taken with benzodiazepines, other sedatives, alcohol, illicit drugs such as heroin, or other opioids.
- Discuss the importance of periodic reassessment to ensure that opioids are helping to meet patient goals and to allow opportunities for opioid discontinuation and consideration of alternative treatment options if opioids are not effective or are harmful.
- Discuss planned use of precautions to reduce risks, including use of prescription drug monitoring program information (see Recommendation 9) and urine drug testing (see Recommendation 10). Consider including discussion of naloxone use for overdose reversal (see Recommendation 8).
- 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. The importance of reassessing safer medication use should be discussed with both the patient and caregiver.
- Discuss risks to family members and persons in the community 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 (*175*).

Given the possibility that benefits of opioid therapy might diminish or that risks might become more prominent over time, it is important that providers review expected benefits and risks of continued opioid therapy with patients periodically, at least every 3 months (see Recommendation 7).

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

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

ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of opioids such as oxycodone, oxymorphone, hydrocodone, and morphine. The clinical evidence review found a fair-

quality study showing a higher risk for overdose among patients initiating treatment with ER/LA opioids than among those initiating treatment with immediate-release opioids (*65*). The clinical evidence review did not find evidence that continuous, time-scheduled use of ER/LA opioids is more effective or safer than intermittent use of immediate-release opioids or that time-scheduled use of ER/LA opioids reduces risks for opioid misuse or addiction (KQ3).

In 2014, the FDA modified the labeling for ER/LA opioid pain medications, noting serious risks and recommending that ER/LA opioids be reserved for "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment" when "alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain" and not used as "as needed" pain relievers (*109*). FDA has also noted that some ER/LA opioids are only appropriate for opioid-tolerant patients, defined as patients who have received certain dosages of opioids (e.g., 60 mg daily of oral morphine, 30 mg daily of oral oxycodone, or equianalgesic dosages of other opioids) for at least 1 week (*176*). Time-scheduled opioid use can be associated with greater total average daily opioid dosage compared with intermittent, as-needed opioid use (contextual evidence review). In addition, experts indicated that there was not enough evidence to determine the safety of using immediate-release opioids for breakthrough pain when ER/LA opioids are used for chronic pain outside of active cancer pain, palliative care, or end-of-life care, and that this practice might be associated with dose escalation.

Abuse-deterrent technologies have been employed to prevent manipulation intended to defeat extended-release properties of ER/LA opioids and to prevent opioid use by unintended routes of administration, such as injection of oral opioids. As indicated in FDA guidance for industry on evaluation and labeling of abuse-deterrent opioids (*177*), although abuse-deterrent technologies are expected to make manipulation of opioids more difficult or less rewarding, they do not prevent opioid abuse through oral intake, the most common route of opioid abuse, and can still be abused by nonoral routes. The "abuse-deterrent" label does not indicate that there is no risk for abuse. No studies were found in the clinical evidence review assessing the effectiveness of abuse-deterrent technologies as a risk mitigation strategy for deterring or preventing abuse. In addition, abuse-deterrent technologies do not prevent unintentional overdose through oral intake. Experts agreed that recommendations could not be offered at this time related to use of abuse-deterrent formulations.

In comparing different ER/LA formulations, the clinical evidence review found inconsistent results for overdose risk with methadone versus other ER/LA opioids used for chronic pain (KQ3). The contextual evidence review found that methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for chronic pain. In addition, methadone is associated with cardiac arrhythmias along with QT prolongation on the electrocardiogram, and it has complicated pharmacokinetics and pharmacodynamics, including a long and variable half-life and peak respiratory depressant effect occurring later and lasting longer than peak analgesic effect. Experts noted that the pharmacodynamics of methadone are subject to more inter-individual variability than other opioids. In regard to other ER/LA opioid formulations, experts noted that the absorption and pharmacodynamics of transdermal fentanyl are complex, with gradually increasing serum concentration during the first part of the 72-hour dosing interval, as well as variable absorption based on factors such as external heat. In addition, the dosing of transdermal fentanyl in mcg/hour, which is not typical for a drug used by outpatients, can be confusing. Experts thought that these complexities might increase the risk for fatal overdose when methadone or transdermal fentanyl is prescribed to a patient who has not used it previously or by providers who are not familiar with its effects.

Experts agreed that for patients not already receiving opioids, providers should not initiate opioid treatment with ER/LA opioids and should not prescribe ER/LA opioids for intermittent use. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who

have received immediate-release opioids daily for at least 1 week. When changing to an ER/LA opioid for a patient previously receiving a different immediate-release opioid, providers should consult product labeling and reduce total daily dosage to account for incomplete opioid cross-tolerance. Providers should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or hepatic dysfunction because decreased clearance of drugs among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations. Although there might be situations in which clinicians need to prescribe immediate-release and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to immediate-release opioids by temporarily using lower dosages of both), in general, avoiding the use of immediate-release opioids in combination with ER/LA opioids is preferable, given potentially increased risk and diminishing returns of such an approach for chronic pain.

When an ER/LA opioid is prescribed, using one with predictable pharmacokinetics and pharmacodynamics is preferred to minimize unintentional overdose risk. In particular, unusual characteristics of methadone and of transdermal fentanyl make safe prescribing of these medications for pain especially challenging.

- Methadone should not be the first choice for an ER/LA opioid. Only providers 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. A clinical practice guideline that contains further guidance regarding methadone prescribing for pain has been published previously (*178*).
- Because dosing effects of transdermal fentanyl are often misunderstood by both providers and patients, only providers 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, providers should prescribe the lowest 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 dosage to ≥90 MME/ day (recommendation category: A, evidence type: 3).

Benefits of high-dose opioids for chronic pain are not established. The clinical evidence review found only one study (*72*) addressing effectiveness of dose titration for outcomes related to pain control, function, and quality of life (KQ3). This randomized trial found no difference in pain or function between a more liberal opioid dose escalation strategy and maintenance of current dosage. (These groups were prescribed average dosages of 52 and 40 MME/day, respectively, at the end of the trial.) At the same time, risks for serious harms related to opioid therapy increase at higher opioid dosage. The clinical evidence review found that higher opioid dosages are associated with increased risks for motor vehicle crashes, opioid abuse or dependence, and overdose (KQ2). The clinical and contextual evidence reviews found that opioid overdose risk increases in a dose-response manner, that dosages of 50–99 MME/day have been found to increase risks for opioid overdose by factors of 1.9 to 4.6 compared with dosages of 1–19 MME/day, and that dosages ≥100 MME/day are associated with increased risks of overdose 2.0–8.9 times the risk at 1–19 MME/day.

The contextual evidence review found that although there is not a single dosage threshold below which overdose risk is eliminated, holding dosages <50 MME/day would likely reduce risk among a large proportion of patients who would experience fatal overdose at higher prescribed dosages. Experts agreed that lower dosages of opioids reduce the risk for overdose, but that a single dosage threshold for safe opioid use could not be identified. Experts noted that daily opioid dosages <50 MME/day are safer than dosages of 50–100 MME/day, and that dosages <20 MME/day are safer than dosages of 20–50

MME/day. Experts agreed that, in general, increasing dosages to 50 or more MME/day increases overdose risk without necessarily adding benefits for pain control or function. Experts also agreed that additional precautions should be taken when patients are prescribed daily opioid dosages of ≥50 MME/day and that opioid dosages generally should not be increased to ≥90 MME/day.

When opioids are used for chronic pain outside of active cancer, palliative, and end-of-life care, providers should start opioids at the lowest possible effective dosage (i.e., the lowest starting dosage on product labeling). Providers should use additional caution when initiating opioids for patients aged ≥65 years and for patients with renal or hepatic insufficiency because decreased clearance of drugs in these patients can result in accumulation of drugs to toxic levels. Providers should use caution when increasing opioid dosages and increase dosage by the smallest practical amount because overdose risk increases with increases in opioid dosage. Although there is limited evidence to recommend specific intervals for dosage titration, a previous guideline recommended waiting at least five half-lives before increasing dosage and waiting at least a week before increasing dosage of methadone and fentanyl to make sure that full effects of the previous dosage are evident (*25*). Providers should re-evaluate patients after increasing dosage (see Recommendation 7). If a patient's opioid dosage for all sources of opioids combined reaches or exceeds 50 MME/day, providers should reassess the patient's pain, function, and treatment and should implement additional precautions, including increased frequency of follow-up (see Recommendation 7). Providers should take additional steps to mitigate overdose risk for patients receiving total daily opioid dosages of ≥50 MME/day, such as considering offering naloxone and overdose prevention education to both patients and the patients' household members (see Recommendation 8). Providers should generally avoid increasing opioid dosages to ≥90 MME/day. If patients do not experience improvement in pain and function at ≥90 MME/day, or if there are escalating dosage requirements, providers should discuss other approaches to pain management with the patient, consider working with patients to taper and discontinue opioids (see Recommendation 7), and should consider consulting a pain specialist. Some states require providers to implement clinical protocols at specific dosage levels; providers should be aware of rules related to MME thresholds and associated clinical protocols established by their states.

Established patients already taking high dosages of opioids, as well as patients transferring from other providers, might consider the possibility of opioid dosage reduction to be anxiety-provoking, and tapering opioids can be especially challenging after years on high dosages because of physical and psychological dependence. However, these patients should be offered the opportunity to re-evaluate their continued use of opioids at high dosages in light of recent evidence regarding the association of opioid dosage and overdose risk. Providers should explain in a nonjudgmental manner to patients already taking high opioid dosages (≥90 MME/day) that there is now an established body of scientific evidence showing that overdose risk is increased at higher opioid dosages. Providers should empathically review benefits and risks of continued high-dosage opioid therapy and should offer to work with the patient to taper opioids to safer dosages. For patients who agree to taper opioids to lower dosages, providers should collaborate with the patient on a tapering plan (see Recommendation 7). Experts noted that patients tapering opioids after taking them for years might require very slow opioid tapers as well as pauses in the taper to allow gradual accommodation to lower opioid dosages. Providers should remain alert to signs of anxiety, depression, and opioid use disorder (see Recommendations 8 and 12) that might be unmasked by an opioid taper and arrange for management of these co-morbidities. For patients agreeing to taper to lower opioid dosages as well as for those remaining on high opioid dosages, providers should establish goals with the patient for continued opioid therapy (see Recommendation 2), maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 1), and consider consulting a pain specialist as needed to assist with pain management.

DRAFT

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 immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three or fewer days usually will be sufficient for most nontraumatic pain not related to major surgery (recommendation category: A, evidence type: 4).

The clinical evidence review found that opioid use for acute pain (i.e., pain with abrupt onset and caused by an injury or other process that is not ongoing) is associated with long-term opioid use, and that a greater amount of early opioid exposure is associated with greater risk for long-term use (KQ5). Several guidelines on opioid prescribing for acute pain from emergency departments (*179–181*) and other settings (*182,183*) have recommended prescribing ≤3 days of opioids in most cases, whereas others have recommended <7 days (*184*) or <14 (*26*) days. Because physical dependence on opioids is an expected physiologic response in patients exposed to opioids for more than a few days (contextual evidence review), limiting days of opioids prescribed also should minimize the need to taper opioids to prevent distressing or unpleasant withdrawal symptoms. Experts noted that more than a few days of exposure to opioids significantly increases hazards and also that prescriptions with fewer days' supply will minimize the number of pills available for unintentional or intentional diversion.

Experts agreed that when opioids are needed for acute pain, providers should prescribe opioids at the lowest effective dose and for no longer than the expected duration of pain severe enough to require opioids to minimize unintentional initiation of long-term opioid use. The lowest effective dose can be determined using product labeling as a starting point with calibration as needed based on the severity of pain and on other clinical factors such as renal or hepatic insufficiency (see Recommendation 8). Experts thought, based on clinical experience regarding anticipated duration of pain severe enough to require an opioid, that in most cases of acute pain not related to major surgery or trauma, a ≤3 days' supply of opioids will be sufficient. For example, in one study of the course of acute low back pain (not associated with malignancies, infections, spondylarthropathies, fractures, or neurological signs) in a primary care setting, there was a large decrease in pain until the fourth day after treatment with paracetamol, with smaller decreases thereafter (*185*). Providers should consider a default of ≤3 days of opioids for acute pain and adjust the duration based on the circumstances of the pain syndrome. Providers should not prescribe additional opioids to patients "just in case" pain continues longer than expected. Providers should re-evaluate 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. Given longer half-lives and longer duration of effects (e.g., respiratory depression) with LA/ER opioids such as methadone, fentanyl patches, or extended release versions of opioids such as oxycodone, oxymorphone, or morphine, providers should not prescribe ER/LA opioids for the treatment of acute pain.

7. Providers should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Providers 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, providers should work with patients to reduce opioid dosage and to discontinue opioids (recommendation category: A, evidence type: 4).

Although the clinical evidence review did not find studies evaluating the effectiveness of more frequent monitoring intervals (KQ4), it did find that continuing opioid therapy for 3 months substantially increases risk for opioid use disorder (KQ2); therefore, follow-up earlier than 3 months might be necessary to provide the greatest opportunity to prevent the development of opioid use disorder. In addition, risk for overdose associated with ER/LA opioids might be particularly high during the first 2 weeks of treatment (KQ3). The contextual evidence review found that patients who do not have pain relief with opioids at 1 month are unlikely to experience pain relief with opioids at 6 months. Although evidence is insufficient to determine at what point within the first 3 months of opioid therapy the risks

DRAFT

for opioid use disorder increase, reassessment of pain and function within 1 month of initiating opioids provides an opportunity to minimize risks of long-term opioid use by discontinuing opioids among patients not receiving a clear benefit from these medications. Experts noted that risks for opioid overdose are greatest during the first 3–7 days after opioid initiation or increase in dosage, particularly when methadone or transdermal fentanyl are prescribed; that follow-up within 3 days is appropriate when initiating or increasing the dosage of methadone; and that follow-up within 1 week might be appropriate when initiating or increasing the dosage of other ER/LA opioids.

Providers 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. Providers should 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/day. Shorter follow-up intervals (within 3 days) should be strongly considered when starting or increasing the dosage of methadone. At follow up, providers should assess benefits in function, pain control, and quality of life using tools such as the 3-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale (*173*) and/or asking patients about progress toward functional goals that have meaning for them (see Recommendation 2). Providers should also ask patients about common adverse effects such as constipation and drowsiness (see Recommendation 3), as well as asking about and assessing for effects that might be early warning signs for more serious problems such as overdose (e.g., sedation, slurred speech, ataxia) or opioid use disorder (e.g., craving, wanting to take opioids in greater quantities or more frequently than prescribed, difficulty controlling use). Providers should ask patients about their preferences for continuing opioids, given their effects on pain and function relative to any adverse effects experienced.

Because of potential changes in the balance of benefits and risks of opioid therapy over time, providers should regularly reassess all patients receiving long-term opioid therapy at least every 3 months. At reassessment, providers 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 early warning signs of serious adverse events, signs of opioid use disorder (e.g., difficulty controlling use, work or family problems related to opioid use), whether benefits of opioids continue to outweigh risks, and whether opioid dosage can be reduced or opioids can be discontinued. Ideally, these reassessments would take place in person and be conducted by the prescribing provider. In practice contexts where virtual visits are part of standard care (e.g., in remote areas where distance or other issues make follow-up visits challenging), follow-up assessments that allow the provider to communicate with and observe the patient through video and audio could be conducted, with in-person visits occurring at least once per year. Providers should re-evaluate patients who are exposed to greater risk (e.g., patients with depression or other mental health conditions, history of substance use disorder, taking ≥50 MME/day) more frequently than every 3 months. If clinically meaningful improvements in pain and function are not sustained, if patients are on high-risk regimens (e.g., dosages ≥50 MME/day or opioids combined with benzodiazepines) without evidence of benefit, if patients believe benefits no longer outweigh risks or if they request dosage reduction or discontinuation, or if patients experience overdose or other serious adverse events (e.g., an event leading to hospitalization or disability) or warning signs of serious adverse events, providers should work with patients to reduce opioid dosage and to discontinue opioids when possible. Providers should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 1) and consider consulting a pain specialist as needed to assist with pain management.

Considerations for Tapering Opioids

Although the clinical evidence review did not find high-quality studies comparing the effectiveness of different tapering protocols for use when opioid dosage is reduced or opioids are discontinued (KQ3), tapers reducing weekly dosage by 10%–50% of the original dosage have been recommended by other

DRAFT

clinical guidelines (*186*), and a rapid taper over 2–3 weeks has been recommended in the case of a severe adverse event such as overdose (*26*). Experts noted that tapers slower than 10% per week (e.g., 10% per month) might also be appropriate and better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations (e.g., for years). Opioid withdrawal during pregnancy has been associated with spontaneous abortion and premature labor.

When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., drug craving, anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should be used. A decrease of 10% of the original dose per week is a reasonable starting point; experts agreed that tapering plans may be individualized based on patient goals and concerns. Experts noted that at times, tapers might have to be paused and restarted again when the patient is ready and might have to be slowed once patients reach low dosages. Tapers may be considered successful as long as the patient is making progress. Once the smallest available dose is reached, the interval between doses can be extended. Opioids may be stopped when taken less frequently than once a day. More rapid tapers might be needed for patient safety under certain circumstances (e.g., for patients who have experienced overdose on their current dosage). Ultrarapid detoxification under anesthesia is associated with substantial risks, including death, and should not be used (*187*). Providers should access 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. Patients who are not taking opioids (including patients who are diverting all opioids they obtain) do not require tapers. Providers should discuss with patients undergoing tapering the increased risk for overdose on abrupt return to a previously prescribed higher dose. Nonopioid pain management (see Recommendation 1), as well as psychosocial support for anxiety related to the taper, should be optimized. More detailed guidance on tapering, including management of withdrawal symptoms has been published previously (*26,188*). If a patient exhibits signs of opioid use disorder (dependence, addiction), providers should offer or arrange for treatment of opioid use disorder (see Recommendation 12) and consider offering naloxone for overdose prevention (see Recommendation 8).

Assessing Risk and Addressing Harms of Opioid Use

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).

The clinical evidence review found insufficient evidence to determine how harms of opioids differ depending on patient demographics or patient comorbidities (KQ2). However, based on the contextual evidence review and expert opinion, certain risk factors are likely to increase susceptibility to opioid-associated harms and warrant incorporation of additional strategies into the management plan to mitigate risk. Providers should assess these risk factors periodically, with frequency varying by risk factor and patient characteristics. For example, factors that vary more frequently over time, such as alcohol use, require more frequent follow up.

Patients with Sleep-Disordered Breathing, Including Sleep Apnea

Risk factors for sleep-disordered breathing include congestive heart failure, and obesity. Experts noted that careful monitoring and cautious dose titration should be used if opioids are prescribed for patients with mild sleep-disordered breathing. Providers should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing whenever possible to minimize risks for opioid overdose (contextual evidence review).

DRAFT

Pregnant Women

Opioid therapy during pregnancy has been associated with stillbirth, poor fetal growth, pre-term delivery, neonatal opioid withdrawal syndrome, and birth defects (contextual evidence review). Providers and patients should together carefully weigh risks and benefits when making decisions about whether to initiate opioid therapy for chronic pain during pregnancy. In addition, before initiating opioid therapy for chronic pain for reproductive-age women, providers should discuss family planning and how chronic opioid use might affect any future pregnancy. For pregnant women already receiving opioids, providers should access appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal (see Recommendation 7). For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine or methadone has been associated with improved maternal outcomes and should be offered (*189*) (see Recommendation 12). Providers caring for pregnant women receiving opioids for pain or receiving buprenorphine or methadone for opioid use disorder should arrange for delivery at a facility prepared to monitor, evaluate for, and treat neonatal opioid withdrawal syndrome. Neonatal toxicity and death have been reported in breast-feeding infants whose mothers are taking codeine (contextual evidence review); previous guidelines have recommended that codeine be avoided whenever possible among mothers who are breast feeding and, if used, should be limited to the lowest possible dose and to a 4-day supply (*190*).

Patients with Renal or Hepatic Insufficiency

Providers should use additional caution and increased monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency, given their decreased ability to process and excrete drugs, susceptibility to accumulation of opioids, and reduced therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (contextual evidence review; see Recommendations 4, 5, and 7).

Patients Aged ≥65 Years

Given reduced renal function and medication clearance even in the absence of renal disease, patients aged ≥65 years might have increased susceptibility to accumulation of opioids and a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (contextual evidence review). Some older adults suffer from cognitive impairment, which can increase risk for medication errors and make opioid-related confusion more dangerous. In addition, older adults are more likely than younger adults to experience co-morbid medical conditions and more likely to receive multiple medications, some of which might interact with opioids (such as benzodiazepines). Providers should use additional caution and increased monitoring (see Recommendations 4, 5, and 7) to minimize risks of opioids prescribed for patients aged ≥65 years. Experts suggested that providers educate older adults receiving opioids to avoid risky medication-related behaviors such as obtaining controlled medications from multiple prescribers and saving unused medications. Providers should also implement interventions to mitigate common risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.

Patients with Mental Health Conditions

Because psychological distress frequently interferes with improvement of pain and function in patients with chronic pain, using validated instruments such as the Generalized Anxiety Disorder (GAD)-7 and the Patient Health Questionnaire (PHQ)-9 or the PHQ-4 to assess for anxiety, post-traumatic stress disorder, and/or depression (*191*), might help providers improve overall pain treatment outcomes. Experts noted that providers should use additional caution and increased monitoring (see Recommendation 7) to lessen the increased risk for opioid use disorder among patients with mental health conditions (including depression, anxiety disorders, and PTSD), as well as increased risk for drug overdose among patients with depression. Previous guidelines have noted that opioid therapy should not

DRAFT

be initiated during acute psychiatric instability or uncontrolled suicide risk, and that providers should consider behavioral health specialist consultation for any patient with a history of suicide attempt or psychiatric disorder (*25*). In addition, patients with anxiety disorders and other mental health conditions are more likely to receive benzodiazepines, which can exacerbate opioid-induced respiratory depression and increase risk for overdose (see Recommendation 11). Providers should ensure that treatment for depression is optimized. Treatment for depression can improve pain symptoms as well as depression and might decrease overdose risk (contextual evidence review). For treatment of chronic pain in patients with depression, providers should strongly consider using tricyclic or SNRI antidepressants for analgesic as well as antidepressant effects if these medications are not otherwise contraindicated (see Recommendation 1).

Patients with Substance Use Disorder

Illicit drugs and alcohol are listed as contributory factors on a substantial proportion of death certificates for opioid-related overdose deaths (contextual evidence review). Previous guidelines have recommended screening or risk assessment tools to identify patients at higher risk for misuse or abuse of opioids. However, the clinical evidence review found that currently available risk-stratification tools (e.g., Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain Version 1, SOAPP-R, and Brief Risk Interview) show insufficient accuracy for classification of patients as at low risk for abuse or misuse (KQ4). Providers should always exercise caution when considering or prescribing opioids for any patient with chronic pain outside of active cancer, palliative, and end-of-life care and should not overestimate the ability of these tools to rule out risks from long-term opioid therapy.

Providers should ask patients about their drug and alcohol use. Single screening questions can be used (*192*). For example, the question "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" (with an answer of one or more considered positive) was found in a primary care setting to be 100% sensitive and 73.5% specific for the detection of a drug use disorder compared with a standardized diagnostic interview (*193*). Validated screening tools such as the Drug Abuse Screening Test (DAST) (*194*) and the Alcohol Use Disorders Identification Test (AUDIT) (*195*) can also be used. Providers should use PDMP data (see Recommendation 9) and drug testing (see Recommendation 10) as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and overdose. Providers should also provide specific counseling on increased risks for overdose when opioids are combined with other drugs or alcohol (see Recommendation 3) and ensure that patients receive effective treatment for substance use disorders when needed (see Recommendation 12).

The clinical evidence review found insufficient evidence to determine how harms of opioids differ depending on past or current substance use disorder (KQ2), although a history of substance use disorder was associated with misuse. Similarly, based on contextual evidence, patients with drug or alcohol use disorders are likely to experience greater risks for opioid abuse and overdose than persons without these conditions. If providers consider opioid therapy for chronic pain outside of active cancer, palliative, and end-of-life care for patients with drug or alcohol use disorders, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone (see Offering naloxone to patients when factors that increase risk for opioid-related harms are present) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed. Because pain management in patients with substance use disorder can be complex, providers should consider consulting substance use disorder specialists and pain specialists regarding pain management for persons with active or recent past history of substance abuse. Experts also noted that providers should communicate with patients' substance use disorder treatment providers if opioids are prescribed.

DRAFT

Patients with Prior Nonfatal Overdose

Although studies were not identified that directly addressed the risk for overdose among patients with prior nonfatal overdose who are prescribed opioids, based on clinical experience, experts thought that prior nonfatal overdose would substantially increase risk for future nonfatal or fatal opioid overdose. If patients experience nonfatal opioid overdose, providers should work with them to reduce opioid dosage and to discontinue opioids when possible (see Recommendation 7). If providers continue opioid therapy for chronic pain outside of active cancer, palliative, and end-of-life care in patients with prior opioid overdose, they should discuss increased risks for overdose with patients, carefully consider whether benefits of opioids outweigh substantial risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone (see Offering naloxone to patients when factors that increase risk for opioid-related harms are present) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed.

Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present

Naloxone is an opioid antagonist that can reverse severe respiratory depression; its administration by lay persons, such as friends and family of persons who experience opioid overdose, can save lives. The contextual evidence review did not find any studies on effectiveness of prescribing naloxone for overdose prevention among patients prescribed opioids for chronic pain. However, there is evidence for effectiveness of naloxone provision in preventing opioid-related overdose death at the community level through community-based distribution (e.g., through overdose education and naloxone distribution programs in community service agencies) to persons at risk for overdose (mostly due to illicit opiate use), and it is plausible that effectiveness would be observed when naloxone is provided in the clinical setting as well. Experts agreed that it is preferable not to initiate opioid treatment when factors that increase risk for opioid-related harms are present. Opinions diverged about the likelihood of naloxone being useful to patients and the circumstances under which it should be offered. However, most experts agreed that providers should consider offering naloxone when prescribing opioids to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients taking benzodiazepines with opioids, patients at risk for returning to a high dose to which they are no longer tolerant (e.g., patients recently released from prison), and patients on higher dosages of opioids (≥50 MME/day). Practices should provide education on overdose prevention and naloxone use to patients receiving naloxone prescriptions and to members of their households. Experts noted that naloxone co-prescribing can be facilitated by clinics or practices with resources to provide naloxone training and by collaborative practice models with pharmacists. Resources for prescribing naloxone in primary care settings can be found through Prescribe to Prevent at http://prescribetoprevent.org.

9. Providers 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 high opioid dosages or dangerous combinations that put him or her at high risk for overdose. Providers 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).

PDMPs are state-based databases that collect information on controlled prescription drugs dispensed by pharmacies in most states and, in select states, by dispensing physicians as well. PDMPs do not currently include information on prescriptions dispensed from Veterans' Health Administration facilities and often do not include prescriptions dispensed in other states. Certain states require providers to review PDMP data prior to writing each opioid prescription (see state-level PDMP-related policies on the National Alliance for Model State Drug Laws website at http://www.namsdl.org/prescription-monitoring-programs.cfm). The clinical evidence review did not find studies evaluating the

DRAFT

effectiveness of PDMPs on outcomes related to overdose, addiction, abuse, or misuse (KQ4). However, even though evidence is limited on the effectiveness of PDMP implementation at the state level on prescribing and mortality outcomes (*23*), the contextual evidence review found that most fatal overdoses were associated with patients receiving opioids from multiple prescribers and/or with patients receiving high total daily opioid dosages; information on both of these risk factors for overdose are available to prescribers in the PDMP. PDMP data can also be helpful when patient medication history is not otherwise available (e.g., for patients from other locales) and when patients transition care to a new provider. The contextual evidence review also found that PDMP information could be used in a way that is harmful to patients. For example, it has been used to dismiss patients from provider practices (*196*), which might adversely affect patient safety.

The contextual review found variation in state policies that affect timeliness of PDMP data (and therefore benefits of reviewing PDMP data) as well as time and workload for providers in accessing PDMP data. In states that permit delegating access to other members of the health care team, workload for prescribers can be reduced. These differences might result in a different balance of benefits to provider workload in different states. Experts agreed that PDMPs are useful tools that should be consulted when starting a patient on opioid therapy and periodically during long-term opioid therapy. However, experts disagreed on how frequently providers should check the PDMP during long-term opioid therapy, given PDMP access issues and the lag time in reporting in some states. Most experts agreed that PDMP data should be reviewed every 3 months or more frequently during long-term opioid therapy. A minority of experts noted that, given the current burden of accessing PDMP data in some states and the lack of evidence surrounding the most effective interval for PDMP review to improve patient outcomes, annual review of PDMP data during long-term opioid therapy would be reasonable when factors that increase risk for opioid-related harms are not present.

Providers 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 (e.g., 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 (e.g., provider 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. As vendors and practices facilitate integration of PDMP information into regular clinical workflow (e.g., data made available in electronic health records), providers' ease of access in reviewing PDMP data is expected to improve. In addition, improved timeliness of PDMP data will improve their value in identifying patient risks.

If patients are found to have multiple controlled substance prescriptions written by different providers, several actions can be taken to augment providers' abilities to improve patient safety:

- Providers should discuss information from the PDMP with their patient and confirm that the patient is aware of the additional prescriptions. Occasionally, PDMP information can be incorrect (e.g., if a pharmacist entered the wrong name or birthdate, the patient uses a nickname or maiden name, or another person has used the patient's identity to obtain prescriptions).
- Providers should discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving opioids from more than one prescriber or receiving medications that increase risk when combined with opioids (e.g., benzodiazepines) and consider offering naloxone (see Recommendation 8).
- If patients are receiving benzodiazepines, providers should avoid whenever possible prescribing opioids if not yet started or consider tapering opioids if already initiated (see Recommendations

DRAFT

11 and 7). Alternatively, providers and patients can consider tapering benzodiazepines and using alternative therapies for anxiety. Benzodiazepines should be tapered gradually to minimize risks associated with benzodiazepine withdrawal (see Recommendation 11).

- Providers should calculate the total MME/day for concurrent opioid prescriptions to help assess the patient's overdose risk (see Recommendation 5). If patients are found to be receiving high total daily dosages of opioids, providers should discuss their safety concerns with the patient, consider tapering to a safer dosage (see Recommendations 5 and 7), and consider offering naloxone (see Recommendation 8).
- Providers should discuss safety concerns with other providers who are prescribing controlled substances for their patient. Ideally providers should first discuss concerns with their patient and inform him or her that they plan to coordinate care with the patient's other prescribers to improve the patient's safety.
- Providers should consider the possibility of a substance use disorder and discuss concerns with their patient (see Recommendation 12).
- If providers suspect their patient might be sharing or selling opioids and not taking them, providers should consider urine drug testing to assist in determining whether opioids can be discontinued without causing withdrawal (see Recommendations 7 and 10). A negative drug test for prescribed opioids might indicate the patient is not taking prescribed opioids, although providers should consider other possible reasons for this test result (see Recommendation 10).

Experts agreed that providers should not dismiss patients from their practice on the basis of PDMP information. Doing so can adversely affect patient safety, could represent patient abandonment, and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of opioids and overdose prevention) and interventions (e.g., safer prescriptions, nonopioid pain treatment [see Recommendation 1], naloxone [see Recommendation 8], and effective treatment for substance use disorder [see Recommendation 12]).

10. When prescribing opioids for chronic pain, providers 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).

Concurrent use of opioid pain medications with other opioid pain medications, benzodiazepines, or heroin can increase patients' risk for overdose. Urine drug tests can provide information about drug use that is not reported by the patient. In addition, urine drug tests can assist providers in identifying when patients are not taking opioids prescribed for them, which might in some cases indicate diversion or other clinically important issues such as difficulties with adverse effects. Urine drug tests do not provide accurate information about how much or what dose of opioids or other drugs a patient took. The clinical evidence review did not find studies evaluating the effectiveness of urine drug screening for risk mitigation during opioid prescribing for pain (KQ4). The contextual evidence review found that urine drug testing can provide useful information about patients assumed not to be using unreported drugs. Urine drug testing results can be subject to misinterpretation and might sometimes be associated with practices that might harm patients (e.g., stigmatization, inappropriate termination from care). Routine use of urine drug tests with standardized policies at the practice or clinic level might destigmatize their use. Although random drug testing might also destigmatize urine drug testing, experts thought that truly random testing was not feasible in clinical practice. Some clinics obtain a urine specimen every visit, but only send it for testing on a random schedule. Experts noted that in addition to direct costs of urine drug testing, which are often not fully covered by insurance and can be a burden for patients, provider time is needed to interpret, confirm, and communicate results.

DRAFT

Experts agreed that prior to starting opioids for chronic pain and periodically during opioid therapy, providers 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. While experts agreed that providers should use urine drug testing before initiating opioid therapy for chronic pain, they disagreed on how frequently urine drug testing should be conducted during long-term opioid therapy. Most experts agreed that urine drug testing at least annually for all patients was reasonable. Some experts noted that this interval might be too long in some cases and too short in others, and that the follow-up interval should be left to the discretion of the provider. Previous guidelines have recommended more frequent urine drug testing in patients thought to be at higher risk for substance use disorder. However, experts thought that predicting risk prior to urine drug testing is challenging and that currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use disorder. Testing of urine is preferred over testing of saliva given that urine drug testing allows for a longer window of detection of drug use (*197*).

Providers should be familiar with the drugs included in urine drug testing panels used in their practice and should understand how to interpret results for these drugs. For example, a positive "opiates" immunoassay detects morphine, which might reflect patient use of morphine, codeine, or heroin, but this immunoassay does not detect synthetic opioids (e.g., fentanyl, methadone) and might not detect semisynthetic opioids (e.g., oxycodone). However, many laboratories use an oxycodone immunoassay that detects oxycodone and oxymorphone. In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is taking and might not mean the patient is taking the specific opioid for which the test was positive. For example, hydromorphone is a metabolite of hydrocodone, and oxymorphone is a metabolite of oxycodone. Detailed guidance on interpretation of urine drug test results, including which tests to order and expected results, drug detection time in urine, drug metabolism, and other considerations has been published previously (*26*). Providers should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. For example, experts noted that there might be uncertainty about the clinical implications of a positive urine drug test for tetrahyrdocannabinol (THC). Before ordering urine drug testing, providers should have a plan for responding to unexpected results. Providers should explain to patients that urine drug testing is intended to improve their safety and should also explain expected results (e.g., presence of prescribed medication and absence of drugs, including illicit drugs, not reported by the patient). Providers should ask patients about use of prescribed and other drugs and ask whether there might be unexpected results. This will provide an opportunity for patients to provide information about changes in their use of prescribed opioids or other drugs. Providers should discuss unexpected results with the local laboratory or toxicologist and with patients. Discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit. If unexpected results are not explained, they should be verified with more specific confirmatory testing that uses gas or liquid chromatography/mass spectrometry.

Providers should use unexpected results to improve patient safety (e.g., change in pain management strategy [see Recommendation 1], tapering or discontinuation of opioids [see Recommendation 7], more frequent re-evaluation [see Recommendation 7], offering naloxone [see Recommendation 8], or referral for treatment for substance use disorder [see Recommendation 12], all as appropriate). Providers should not terminate patients from care based on a urine drug test result because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids from alternative sources and the provider missing opportunities to facilitate treatment for substance use disorder.

DRAFT

11. Providers should avoid prescribing opioid pain medication for patients receiving benzodiazepines whenever possible (recommendation category: A, evidence type: 3).

Benzodiazepines and opioids both cause central nervous system depression and can decrease respiratory drive. Concurrent use is likely to put patients at greater risk for potentially fatal overdose. The clinical evidence review did not address risks of benzodiazepine co-prescription among patients prescribed opioids. However, the contextual evidence review found evidence in epidemiologic series of concurrent benzodiazepine use in large proportions of opioid-related overdose deaths, and a case-cohort study found concurrent benzodiazepine prescription with opioid prescription to be associated with a near quadrupling of risk for overdose death compared with opioid prescription alone (*198*). Experts agreed that although there are circumstances when it might be appropriate to prescribe opioids to a patient receiving benzodiazepines (e.g., severe acute pain in a patient on long-term, stable low-dose benzodiazepine therapy), providers should avoid prescribing opioids for patients receiving benzodiazepines whenever possible. Because of greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and because tapering opioids can be associated with anxiety, when patients receiving both benzodiazepines and opioids require tapering to reduce risk for fatal respiratory depression, it might be safer and more practical to taper opioids first (see Recommendation 7). Providers should taper benzodiazepines gradually if discontinued because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death (contextual evidence review). A commonly used tapering schedule that has been used safely and with moderate success is a reduction of the benzodiazepine dose by 25% every 1–2 weeks (*199*,*200*). CBT increases tapering success rates and might be particularly helpful for patients struggling with a benzodiazepine taper (*199*). If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific anti-depressants or other nonbenzodiazepine medications approved for anxiety should be offered. Experts emphasized that providers should communicate with mental health professionals managing the patient to coordinate care.

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).

Opioid use disorder (previously classified as opioid abuse or opioid dependence) is defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) as a problematic pattern of opioid use leading to clinically significant impairment or distress, manifested by at least two defined criteria occurring within a year (see http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf) (*16*).

The clinical evidence review found prevalence of opioid dependence in primary care settings among patients with chronic pain on opioid therapy to be 3%–26% (KQ2). As found in the contextual evidence review and supported by moderate quality evidence, opioid agonist or partial agonist treatment with methadone maintenance therapy or buprenorphine in combination with psychosocial treatment has been shown to be more effective in preventing relapse among patients with opioid use disorder than detoxification without maintenance medication (*141–144*). However, the cited studies primarily evaluated patients with a history of illicit opioid use, rather than prescription opioid use for chronic pain, and studies of referral to treatment from primary care after opioid therapy for chronic pain are limited (*201*,*202*); thus, the evidence of effectiveness for referral to treatment for opioid dependence in patients with chronic pain is indirect and graded as low (type 3). Treatment need in a community is often not met by capacity to provide buprenorphine or methadone maintenance therapy (*203*), and patient cost can be a barrier to buprenorphine treatment because insurance coverage of buprenorphine for opioid use disorder is often limited (*204*). Oral or long-acting injectable formulations of naltrexone can also be used as medication-assisted treatment for opioid use disorder in nonpregnant adults, particularly for highly

motivated persons (*205,206*). Experts agreed that providers prescribing opioids should identify treatment resources for opioid use disorder in the community and should work together to ensure sufficient treatment capacity for opioid use disorder at the practice level.

If providers suspect opioid use disorder based on patient concerns or behaviors or on findings in prescription drug monitoring program data (Recommendation 9) or from urine drug testing (Recommendation 10), they should discuss their concern with their patient and provide an opportunity for the patient to disclose related concerns or problems. Providers should assess for the presence of opioid use disorder using DSM-5 criteria (*16*). Alternatively, providers can arrange for a substance use disorder treatment specialist to assess for the presence of opioid use disorder. For patients meeting criteria for opioid use disorder, providers should offer or arrange for patients to receive evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone maintenance therapy in combination with behavioral therapies). Providers should also consider offering naloxone to patients with opioid use disorder (see Recommendation 8). For patients with problematic opioid use that does not meet criteria for opioid use disorder, experts noted that providers can offer to taper and discontinue opioids (see Recommendation 7). For patients who choose to but are unable to taper, providers may reassess for opioid use disorder and offer opioid agonist therapy if criteria are met.

Physicians not already certified to provide buprenorphine in an office-based setting can undergo training to receive 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. Physicians prescribing opioids in communities without sufficient treatment capacity for opioid use disorder should strongly consider obtaining this waiver. Information about qualifications and the process to obtain a waiver are available from SAMHSA (*207*). Additional guidance has been published previously (*208*) on induction, use, and monitoring of buprenorphine treatment for opioid use disorder (see part 5) and on goals, components of, and types of effective psychosocial treatment that are recommended in conjunction with pharmacological treatment of opioid use disorder (see Part 7).

Providers 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 buprenorphine treatment provider or an opioid treatment program specialist, who can provide medication-assisted therapy. Providers should assist patients in finding qualified treatment providers and should arrange for patients to follow up with these providers, as well as arranging for ongoing coordination of care. Providers should not dismiss patients from their practice because of a substance use disorder because this can adversely affect patient safety and could represent patient abandonment. Identification of substance use disorder represents an opportunity for a provider to initiate potentially life-saving interventions, and it is important for the provider to collaborate with the patient regarding their safety to increase the likelihood of successful treatment. In addition, although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Providers should continue to use nonpharmacologic and nonopioid pharmacologic pain treatments as appropriate (see Recommendation 1) and consider consulting a pain specialist as needed to provide optimal pain management.

Resources to help with arranging for treatment include SAMHSA's buprenorphine physician locator (http://buprenorphine.samhsa.gov/bwns_locator/); SAMHSA's Opioid Treatment Program Directory (http://dpt2.samhsa.gov/treatment/directory.aspx); SAMHSA's Provider Clinical Support System for Opioid Therapies (http://pcss-o.org), which offers extensive experience in the treatment of substance use disorders and specifically of opioid use disorder, as well as expertise on the interface of pain and opioid misuse; and SAMHSA's Provider's Clinical Support System for Medication-Assisted Treatment

(http://pcssmat.org), which offers expert physician mentors to answer questions about assessment for and treatment of substance use disorders.

Conclusions and Future Directions

Clinical guidelines represent one strategy for improving prescribing practices and health outcomes. Efforts are required to disseminate the guideline and achieve widespread adoption and implementation of the recommendations in clinical settings. CDC will translate this guideline into user-friendly materials for distribution and use by health systems, medical professional societies, insurers, public health departments, health information technology developers, and providers and engage in dissemination efforts. Activities such as development of clinical decision support in electronic health records to assist providers' treatment decisions at the point of care, identification of mechanisms that insurers and pharmacy benefit plan managers can use to promote safer prescribing within plans, provider education, and development of clinical quality improvement measures and initiatives to improve prescribing and patient care within health systems have promise for increasing guideline adoption and improving practice. In addition, policy initiatives that address barriers to implementation of the guidelines, such as accessibility of PDMP data, availability of providers of medication-assisted treatment for opioid use disorder, insurance coverage for nonpharmacologic treatments and appropriate urine drug testing, and reimbursable time for patient counseling might likewise be effective in enhancing implementation of the recommended practices. As highlighted in the forthcoming report on the National Pain Strategy, an overarching federal effort that outlines a comprehensive population-level health strategy for addressing pain as a public health problem, clinical guidelines complement other strategies aimed at preventing illnesses and injuries that lead to pain. These strategies include strengthening the evidence base for pain prevention and treatment strategies, reducing disparities in pain treatment, improving service delivery and reimbursement, supporting professional education and training, and providing public education. It is important that overall improvements be made in developing the workforce to address pain management in general, in addition to opioid prescribing specifically.

This guideline provides recommendations that are based on the best available evidence that was interpreted and informed by expert opinion. The clinical scientific evidence informing the recommendations is low in quality. To inform future guideline development, more research is necessary to fill in critical evidence gaps. The evidence reviews forming the basis of this guideline clearly illustrate that there is much yet to be learned about the effectiveness, safety, and economic efficiency of long-term opioid therapy. As highlighted by an expert panel in a recent workshop sponsored by the National Institutes of Health on the role of opioid pain medications in the treatment of chronic pain, "evidence is insufficient for every clinical decision that a provider needs to make about the use of opioids for chronic pain" (*209*). The National Institutes of Health panel recommended that research is needed to improve our 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 multidisciplinary pain interventions; estimate cost-benefit; 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. Research that contributes to safer and more effective pain treatment can be implemented across public health entities and federal agencies (*4*). Additional research can inform the development of future guidelines for special populations that could not be adequately addressed in this guideline, such as children and adolescents, where evidence and guidance is needed but currently lacking. Yet, given that chronic pain is recognized as 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 the evidence that is currently available. The tradeoff between

DRAFT

the benefits and the risks 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. CDC will revisit this guideline as needed to determine if evidence gaps have been sufficiently closed to warrant an update of the guideline. Until this research is conducted, clinical practice guidelines will have to be based on the best available evidence and expert opinion. This guideline 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 abuse, dependence, overdose, and death.

Acknowledgments

Members of the Core Expert Group; the Core Expert Group facilitator: Don Teater; members of the Stakeholder Review Group; peer reviewers; federal partners: Richard Kronick, PhD, Deborah G. Perfetto, PharmD, Agency for Healthcare Research and Quality; Jeffrey A. Kelman, MD, Diane L. McNally, Centers for Medicare & Medicaid Services; Jonathan Woodson, MD, Dave Smith, MD, Jack Smith, MD, Christopher Spevak, MD, Department of Defense; Stephen M. Ostroff, MD, Christopher M. Jones, PharmD, Food and Drug Administration; Jim Macrae, MA, MPP, Alexander F. Ross, ScD, Health Resources and Services Administration; Nora Volkow, MD, David Thomas, PhD, National Institute of Drug Abuse; John Howard, MD, National Institute for Occupational Safety and Health Douglas Trout, MD, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Karen B. DeSalvo, MD, Jennifer Frazier, MPH, Office of the National Coordinator, Michael Botticelli, MEd, Cecelia McNamara Spitznas, PhD, Office of National Drug Control Policy, Kana Enomoto, MA, Jinhee Lee, PharmD, Substance Abuse and Mental Health Services Administration; Robert McDonald, MBA, Jack M. Rosenberg, MD, Veterans Administration; constituents who provided comment during the webinar; Abt Associates Douglas McDonald, PhD, Brandy Wyant, MPH, Kenneth Carlson, and Amy Berninger, MPH; and CDC colleagues: Thomas Frieden, MD, Anne Schuchat, MD, Ileana Arias, PhD, Debra Houry, MD, National Center for Injury Prevention and Control, Amy Peeples, MPA, National Center for Injury Prevention and Control, Grant Baldwin, PhD, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Rita Noonan, PhD, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Julie Gilchrist, MD, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Terry Davis, EdD, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Wes Sargent, EdD, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Brian Manns, PharmD, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Lisa Garbarino, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Donovan Newton, MPA, Division of Analysis, Research and Practice Integration, National Center for Injury Prevention and Control, Joann Kang, JD, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Noah Aleshire, JD, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Jennifer VanderVeur, JD, Division for Heart Disease and Stroke Prevention, National Center for Chronic Disease Prevention and Health Promotion LeShaundra Scott, MPH, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Sarah Lewis, MPH, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Helen Kingery, MPH, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Kristen Sanderson, MPH, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Kate Fox, MPP, National Center for Injury Prevention and Control, Leslie Dorigo, MA, National Center for Injury Prevention and Control, Erin Connelly, MPA, National Center for Injury Prevention and Control, Sara Patterson, MA, National Center for Injury Prevention and Control, Mark Biagioni, MPA,

DRAFT

National Center for Injury Prevention and Control, and Leonard J. Paulozzi, MD, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control.

*A list of the members appears on page 51.

References

1. Daubresse M, Chang HY, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000–2010. Med Care 2013;51:870–8.
2. Paulozzi LJ, Mack KA, Hockenberry JM. Vital signs: variation among states in prescribing of opioid pain relievers and benzodiazepines—United States, 2012. MMWR Morb Mortal Wkly Rep 2014;63:563–8.
3. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007–2012. Am J Prev Med 2015;49:409–13.
4. Institute of Medicine. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: The National Academies Press; 2011.
5. International Association for the Study of Pain. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Pain 1986;3:S1–6.
6. Hardt J, Jacobsen C, Goldberg J, et al. Prevalence of chronic pain in a representative sample in the United States. Pain Med 2008;9:803–12.
7. Tsang A, Von Korff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J Pain 2008;9:883–91.
8. Nahin RL. Estimates of pain prevalence and severity in adults, United States, 2012. J Pain 2015;16:769–80.
9. Furlan A, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. Pain Res Manag 2011;16:337–51.
10. Chou R, Deyo R, Devine B, et al. The effectiveness and risks of long-term opioid treatment of chronic pain. Evidence Report/Technology Assessment No. 218. AHRQ Publication No. 14-E005-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2014. Available at http://www.effectivehealthcare.ahrq.gov/ehc/products/557/1971/chronic-pain-opioid-treatment-report-141007.pdf2014.
11. Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf 2009;18:1166–75.
12. CDC. QuickStats: rates of deaths from drug poisoning involving opioid analgesics—United States, 1999–2013. MMWR Morb Mortal Wkly Rep 2015;64:32.
13. National Center for Health Statistics. Health, United States, 2014: with special feature on adults aged 55–64. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2015.
14. CDC. Vital signs: overdoses of prescription opioid pain relievers—United States, 1999–2008. MMWR Morb Mortal Wkly Rep 2011;60:1487–92.
15. Substance Abuse and Mental Health Services Administration. The DAWN report: highlights of the 2011 Drug Abuse Warning Network (DAWN) findings on drug-related emergency department visits. Rockville, MD: US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality; 2013.

DRAFT

16. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

17. Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: summary of national findings. Rockville, MD: US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration; 2014.

18. Edlund MJ, Martin BC, Russo JE, et al. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain. Clin J Pain 2014;30:557–64.

19. Zedler B, Xie L, Wang L, et al. Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. Pain Med 2014;15:1911–29.

20. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 2011;305:1315–21.

21. Jamison RN, Sheehan KA, Scanlan E, Matthews M, Ross EL. Beliefs and attitudes about opioid prescribing and chronic pain management: Survey of primary care providers. J Opioid Manag 2014;10:375–82.

22. Wilson HD, Dansie EJ, Kim MS, Moskovitz BL, Chow W, Turk DC. Clinicians' attitudes and beliefs about opioids survey (CAOS): instrument development and results of a national physician survey. J Pain 2013;14:613–27.

23. Haegerich TM, Paulozzi LJ, Manns BJ, Jones CM. What we know, and don't know, about the impact of state policy and systems-level interventions on prescription drug overdose. Drug Alcohol Depend 2014;145:34–47.

24. American Pain Society, American Academy of Pain Medicine Opioids Guidelines Panel. Guideline for the use of chronic opioid therapy in chronic noncancer pain: evidence review. Chicago, IL: American Pain Society; 2009. Available at http://americanpainsociety.org/uploads/education/guidelines/chronic-opioid-therapy-cncp.pdf.

25. US Department of Veterans Affairs. VA/DoD clinical practice guidelines: management of opioid therapy (OT) for chronic pain (2010). Washington, DC: US Department of Veterans Affairs; 2010. Available at http://www.healthquality.va.gov/guidelines/Pain/cot.

26. Washington State Agency Medical Directors' Group. AMDG 2015 interagency guideline on prescribing opioids for pain. Olympia, WA: Washington State Agency Medical Directors' Group; 2015. Available at http://www.agencymeddirectors.wa.gov/guidelines.asp.

27. Nuckols TK, Anderson L, Popescu I, et al. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. Ann Intern Med 2014;160:38–47.

28. Liu Y, Logan JE, Paulozzi LJ, Zhang K, Jones CM. Potential misuse and inappropriate prescription practices involving opioid analgesics. Am J Manag Care 2013;19:648–65.

29. Mack KA, Zhang K, Paulozzi L, Jones C. Prescription practices involving opioid analgesics among Americans with Medicaid, 2010. J Health Care Poor Underserved 2015;26:182–98.

30. Institute of Medicine. Dying in America: improving quality and honoring individual preferences near the end of life. Washington, DC: The National Academies Press; 2015.

31. Cantrill SV, Brown MD, Carlisle RJ, et al. Clinical policy: critical issues in the prescribing of opioids for adult patients in the emergency department. Ann Emerg Med 2012;60:499–525.

32. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248–73.

33. Pennsylvania Department of Health, Department of Drug and Alcohol Programs. Pennsylvania guidelines on the use of opioids in dental practice. Harrisburg, PA: Pennsylvania Department of Drug

DRAFT

and Alcohol Programs; 2015. Available at http://www.ddap.pa.gov/Document%20Library/Prescriber_Guidelines_Dental.pdf.

34. National Heart Lung and Blood Institute. Evidence-based management of sickle cell disease. Expert Panel report. Washington, DC: National Institutes of Health; 2014.

35. Ahmed FUS. Advisory Committee on Immunization Practices handbook for developing evidence-based recommendations. Version 1.2. Atlanta, GA: Centers for Disease Control and Prevention; 2013. Available at http://www.cdc.gov/vaccines/acip/recs/GRADE/about-grade.html#resources.

36. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines 3: rating the quality of evidence. J Clin Epidemiol 2011;64:401–6.

37. Guyatt GH, Oxman AD, Vist G, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.

38. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines 15: going from evidence to recommendation: determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726–35.

39. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64:380–2.

40. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015;162:276–86.

41. Agency for Healthcare Research and Quality. Methods guide for effectiveness and comparative effectiveness reviews. Effective Health Care Program. AHRQ Publication No. 10(13)-EHC063-EF. Rockville, MD: US Department of Health and Human Services, Agency for Healthcare Research and Quality; 2013. Available at www.effectivehealthcare.ahrq.gov.

42. Graham E. The effectiveness and risks of long-term opioid treatment of chronic pain. PROSPERO: international prospective register of systematic reviews. York, UK: University of York; 2014. Available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014007016.

43. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain—development of a typology of chronic pain patients. Drug Alcohol Depend 2009;104:34–42.

44. Boscarino JA, Rukstalis M, Hoffman SN, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. Addiction 2010;105:1776–82.

45. Compton PA, Wu SM, Schieffer B, Pham Q, Naliboff BD. Introduction of a self-report version of the Prescription Drug Use Questionnaire and relationship to medication agreement noncompliance. J Pain Symptom Manage 2008;36:383–95.

46. Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med 2003;4:340–51.

47. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain 2007;8:573–82.

48. Hojsted J, Nielsen PR, Guldstrand SK, Frich L, Sjogren P. Classification and identification of opioid addiction in chronic pain patients. Eur J Pain 2010;14:1014–20.

49. Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: Results of a 3-year registry study. Clin J Pain 2007;23:287–99.

50. Carrington Reid M, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med 2002;17:173–9.

DRAFT

51. Saffier K, Colombo C, Brown D, Mundt MP, Fleming MF. Addiction Severity Index in a chronic pain sample receiving opioid therapy. J Subst Abuse Treat 2007;33:303–11.

52. Schneider JP, Kirsh KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: a quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. J Opioid Manag 2010;6:385–95.

53. Wasan AD, Butler SF, Budman SH, et al. Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? Clin J Pain 2009;25:193–8.

54. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med 2010;152:85–92.

55. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med 2011;171:686–91.

56. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med 2010;25:310–5.

57. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of fracture in adults: a nested case-control study using the general practice research database. Am J Epidemiol 2013;178:559–69.

58. Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiol Drug Saf 2011;20:754–62.

59. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. J Intern Med 2013;273:511–26.

60. Deyo RA, Smith DH, Johnson ES, et al. Prescription opioids for back pain and use of medications for erectile dysfunction. Spine 2013;38:909–15.

61. Rubinstein A, Carpenter DM. Elucidating risk factors for androgen deficiency associated with daily opioid use. Am J Med 2014;127:1195–201.

62. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. JAMA Intern Med 2013;173:196–201.

63. Salzman RT, Roberts MS, Wild J, Fabian C, Reder RF, Goldenheim PD. Can a controlled-release oral dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? J Pain Symptom Manage 1999;18:271–9.

64. Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. Spine 1998;23:2591–600.

65. Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. JAMA Intern Med 2015;175:608–15.

66. Allan L, Richarz U, Simpson K, Slappendel R. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. Spine 2005;30:2484–90.

67. Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Pract 2010;10:416–27.

68. Mitra F, Chowdhury S, Shelley M, Williams G. A feasibility study of transdermal buprenorphine versus transdermal fentanyl in the long-term management of persistent non-cancer pain. Pain Med 2013;14:75–83.

DRAFT

69. Krebs EE, Becker WC, Zerzan J, Bair MJ, McCoy K, Hui S. Comparative mortality among Department of Veterans Affairs patients prescribed methadone or long-acting morphine for chronic pain. Pain 2011;152:1789–95.

70. Hartung DM, Middleton L, Haxby DG, Koder M, Ketchum KL, Chou R. Rates of adverse events of long-acting opioids in a state Medicaid program. Ann Pharmacother 2007;41:921–8.

71. Ray WA, Chung CP, Murray KT, Cooper WO, Hall K, Stein CM. Out-of-hospital mortality among patients receiving methadone for noncancer pain. JAMA Intern Med 2015;175:420–7.

72. Naliboff BD, Wu SM, Schieffer B, et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. J Pain 2011;12:288–96.

73. Cowan DT, Wilson-Barnett J, Griffiths P, Vaughan DJ, Gondhia A, Allan LG. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. Pain Med 2005;6:113–21.

74. Ralphs JA, Williams AC, Richardson PH, Pither CE, Nicholas MK. Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff controlled cocktail methods. Pain 1994;56:279–88.

75. Tennant FS Jr, Rawson RA. Outpatient treatment of prescription opioid dependence: comparison of two methods. Arch Intern Med 1982;142:1845–7.

76. Akbik H, Butler SF, Budman SH, Fernandez K, Katz NP, Jamison RN. Validation and clinical application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). J Pain Symptom Manage 2006;32:287–93.

77. Jones T, Moore T, Levy JL, et al. A comparison of various risk screening methods in predicting discharge from opioid treatment. Clin J Pain 2012;28:93–100.

78. Moore TM, Jones T, Browder JH, Daffron S, Passik SD. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic pain management. Pain Med 2009;10:1426–33.

79. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med 2005;6:432–42.

80. Jones T, Lookatch S, Grant P, McIntyre J, Moore T. Further validation of an opioid risk assessment tool: the Brief Risk Interview. J Opioid Manag 2014;10:353–64.

81. Jones T, Moore T. Preliminary data on a new opioid risk assessment measure: The Brief Risk Interview. J Opioid Manag 2013;9:19–27.

82. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery. Arch Intern Med 2012;172:425–30.

83. Webster BS, Verma SK, Gatchel RJ. Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use. Spine 2007;32:2127–32.

84. Ganann R, Ciliska D, Thomas H. Expediting systematic reviews: methods and implications of rapid reviews. Implement Sci 2010;5:56.

85. Williams A, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev 2012;11.

86. Hayden JA, van Tulder MW, Malmivaara A, Koes BW. Exercise therapy for treatment of non-specific low back pain. Cochrane Database Syst Rev 2005;3.

87. Fransen M, McConnell S, Harmer Alison R, Van der Esch M, Simic M, Bennell Kim L. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2015;1:CD004376.

DRAFT

88. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. Cochrane Database Syst Rev 2014;4: CD007912. doi:10.1002/14651858. CD007912.

89. Busch AJ, Barber KA, Overend TJ, Peloso PM, Schachter CL. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev 2007;4:CD003786.

90. Lee C, Crawford C, Swann S; Active Self-Care Therapies for Pain (PACT) Working Group. Multimodal, integrative therapies for the self-management of chronic pain symptoms. Pain Med 2014;15:S76–85.

91. Kamper SJ, Apeldoorn AT, Chiarotto A, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. BMJ 2015;350:h444.

92. Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005;64:669–81.

93. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:377–88.

94. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16:137–62.

95. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage 2007;15:981–1000.

96. Jordan KM, Arden NK, Doherty M, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62:1145–55.

97. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 2009;57:1331.

98. Chou R, Qaseem A, Snow V. Clinical Efficacy Assessment Subcommittee of the American College of Physicians, American College of Physicians, American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med 2007;147:478.

99. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: Network meta-analysis. BMJ 2011;342:c7086.

100. Food and Drug Administration. FDA drug safety communication: FDA strengthens warning that non-asprin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2015. Available at http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm.

101. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. Am J Med 2009;122(Suppl):S22–32.

102. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17:1113–e88.

103. Moulin DE, Clark AJ, Gilron I, et al. Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society. Pain Res Manag 2007;12:13–21.

104. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of

Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurol (Tokyo) 2011;76:1758–65.

105. Wallen M, Gillies D. Intra-articular steroids and splints/rest for children with juvenile idiopathic arthritis and adults with rheumatoid arthritis. Cochrane Database Syst Rev 2006; (1):CD002824.

106. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006; (2):CD005328.

107. Buchbinder R, Green S, Youd JM. Corticosteroid injections for shoulder pain. Cochrane Database Syst Rev 2003; (1):CD004016.

108. Food and Drug Administration. Epidural corticosteroid injection: drug safety communication. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm394530.htm.

109. Goal of label changes: better prescribing, safer use of opioids. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2013. Available at http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm367660.htm.

110. Von Korff M, Merrill JO, Rutter CM, Sullivan M, Campbell CI, Weisner C. Time-scheduled vs. pain-contingent opioid dosing in chronic opioid therapy. Pain 2011;152:1256–62.

111. Paulozzi L, Mack KA, Jones CM. Vital Signs: Risk for overdose from methadone used for pain relief, United States, 1999–2010. MMWR Morb Mortal Wkly Rep 2012;62:493–7.

112. Gwira Baumblatt JA, Wiedeman C, Dunn JR, Schaffner W, Paulozzi LJ, Jones TF. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. JAMA Intern Med 2014;174:796–801.

113. Paulozzi LJ, Kilbourne EM, Shah NG, et al. A history of being prescribed controlled substances and risk of drug overdose death. Pain Med 2012;13:87–95.

114. Liang Y, Turner BJ. Assessing risk for drug overdose in a national cohort: role for both daily and total opioid dose? J Pain 2015;16:318–25.

115. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med 2010;152:85–92.

116. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med 2011;171:686–91.

117. Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Med 2015. EPub ahead of print.

118. Jones CM, McAninch JK. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. Am J Prev Med 2015;49:493–501.

119. Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med 2003;349:1943–53.

120. Kalso E, Simpson KH, Slappendel R, Dejonckheere J, Richarz U. Predicting long-term response to strong opioids in patients with low back pain: findings from a randomized, controlled trial of transdermal fentanyl and morphine. BMC Med 2007;5:39.

121. Yue HJ, Guilleminault C. Opioid medication and sleep-disordered breathing. Med Clin North Am 2010;94:435–6.

122. Webster LR, Choi Y, Desai H, Webster L, Grant BJB. Sleep-disordered breathing and chronic opioid therapy. Pain Med 2008;9:425–32.

123. Goodman LS, Limberd LE. Goodman and Gilman's The Pharmacologic Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill; 1996.

DRAFT

124. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. J Gerontol 1976;31:155–63.

125. Rolita L, Spegman A, Tang X, Cronstein BN. Greater number of narcotic analgesic prescriptions for osteoarthritis is associated with falls and fractures in elderly adults. J Am Geriatr Soc 2013;61:335–40.

126. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with the use of morphine and opiates. J Intern Med 2006;260:76–87.

127. Spector W, Shaffer T, Potter DE, Correa-de-Araujo R, Rhona Limcangco M. Risk factors associated with the occurrence of fractures in U.S. nursing homes: resident and facility characteristics and prescription medications. J Am Geriatr Soc 2007;55:327–33.

128. Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. Obstet Gynecol 2013;122:838–44.

129. Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011;204:314 e1–11.

130. Whiteman VE, Salemi JL, Mogos MF, Cain MA, Aliyu MH, Salihu HM. Maternal opioid drug use during pregnancy and its impact on perinatal morbidity, mortality, and the costs of medical care in the United States. J Pregnancy 2014;2014:906723.

131. Hadi I, da Silva O, Natale R, Boyd D, Morley-Forster PK. Opioids in the parturient with chronic nonmalignant pain: a retrospective review. J Opioid Manag 2006;2:31–4.

132. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain 2007;129:355–62.

133. Howe CQ, Sullivan MD. The missing 'P' in pain management: how the current opioid epidemic highlights the need for psychiatric services in chronic pain care. Gen Hosp Psychiatry 2014;36:99–104.

134. Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med 2002;17:173–9.

135. Turner BJ, Liang Y. Drug Overdose in a retrospective cohort with non-cancer pain treated with opioids, antidepressants, and/or sedative-hypnotics: interactions with mental health disorders. J Gen Intern Med 2015 Feb 4 ePub ahead of print.

136. Paulozzi L. CDC Grand rounds: prescription drug overdoses—a U.S. epidemic. MMWR Morb Mortal Wkly Rep 2012;61:10–3.

137. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ 2013;346:f174.

138. Coffin P, Banta-Green C. The dueling obligations of opioid stewardship. Ann Intern Med 2014;160:207.

139. Twillman RK, Kirch R, Gilson A. Efforts to control prescription drug abuse: Why clinicians should be concerned and take action as essential advocates for rational policy. CA Cancer J Clin 2014;64:369–76.

140. Cicero TJ, Ellis MS, Surratt HL. Effect of abuse-deterrent formulation of OxyContin. N Engl J Med 2012;367:187–9.

141. Mattick R, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2014;2: 10.1002/14651858.CD002207.pub4.

DRAFT

142. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev 2009;3: 10.1002/14651858.CD002209.pub2.

143. Amato L, Minozzi S, Davoli M, Vecchi S, Ferri MM, Maynet S. Psychosocial and pharmacological treatments for opioid detoxification. Cochrane Database Syst Rev 2008; (4):CD005031 10.1002/14651858.CD005031.pub3.

144. Fullerton CA, Kim M, Thomas CP, et al. Medication-assisted treatment with methadone: assessing the evidence. Psychiatr Serv 2014;65:146–57.

145. Keller CE, Ashrafioun L, Neumann AM, Van Klein J, Fox CH, Blondell RD. Practices, perceptions, and concerns of primary care physicians about opioid dependence associated with the treatment of chronic pain. Subst Abuse 2012;33:103–13.

146. Payne M, Gething M, Moore AA, Reid MC. Primary care providers' perspectives on psychoactive medication disorders in older adults. Am J Geriatr Pharmacother 2011;9:164–72.

147. Hagemeier NE, Gray JA, Pack RP. Prescription drug abuse: a comparison of prescriber and pharmacist perspectives. Subst Use Misuse 2013;48:761–8.

148. Hooten WM, Bruce BK. Beliefs and attitudes about prescribing opioids among healthcare providers seeking continuing medical education. J Opioid Manag 2011;7:417–24.

149. Hwang CS, Turner LW, Krusczewski SP, Kolodny A, Alexander GC. Prescription drug abuse: a national survey of primary care physicans. JAMA Intern Med 2015;175:302–4.

150. Green TC, Mann MR, Bowman SE, et al. How does use of a prescription monitoring program change medical practice? Pain Med 2012;13:1314–23.

151. Ringwalt C, Garrettson M, Alexandridis A. The effects of North Carolina's prescription drug monitoring program on the prescribing behaviors of the state's providers. J Prim Prev 2015;36:131–7.

152. Pergolizzi J, Pappagallo M, Stauffer J, et al. The role of urine drug testing for patients on opioid therapy. Pain Pract 2010;10:497–507.

153. Starrels JL, Wu B, Peyser D, et al. It made my life a little easier: Primary care providers' beliefs and attitudes about using opioid treatment agreements. J Opioid Manag 2014;10:95–102.

154. Smith RJ, Kilaru AS, Perrone J, et al. How, why, and for whom do emergency medicine providers use prescription drug monitoring programs? Pain Med 2015;16:1122–31.

155. Bair MJ, Krebs EE. Why is urine drug testing not used more often in practice? Pain Pract 2010;10:493–6.

156. Mangione MP, Crowley-Matoka M. Improving pain management communication: how patients understand the terms "opioid" and "narcotic". J Gen Intern Med 2008;23:1336–8.

157. Anastassopoulos KP, Chow W, Tapia CI, Baik R, Moskowitz B, Kim MS. Reported side effects, bother, satisfaction, and adherence in patients taking hydrocodone for non-cancer pain. J Opioid Manag 2013;9:97–109.

158. Gregorian RS Jr, Gasik A, Kwong WJ, Voeller S, Kavanagh S. Importance of side effects in opioid treatment: a trade-off analysis with patients and physicians. J Pain 2010;11:1095–108.

159. Moore SK, Guarino H, Acosta MC, et al. Patients as collaborators: using focus groups and feedback sessions to develop an interactive, web-based self-management intervention for chronic pain. Pain Med 2013;14:1730–40.

160. Simmonds MJ, Finley EP, Vale S, Pugh MJ, Turner BJ. A qualitative study of veterans on long-term opioid analgesics: barriers and facilitators to multimodality pain management. Pain Med 2015;16:726–32.

DRAFT

161. Thielke SM, Turner JA, Shortreed SM, et al. Do patient-perceived pros and cons of opioids predict sustained higher-dose use? Clin J Pain 2014;30:93–101.

162. Hansen RN, Oster G, Edelsberg J, Woody GE, Sullivan SD. Economic costs of nonmedical use of prescription opioids. Clin J Pain 2011;27:194–202.

163. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. Pain Med 2011;12:657–67.

164. Inocencio TJ, Carroll NV, Read EJ, Holdford DA. The economic burden of opioid-related poisoning in the United States. Pain Med 2013;14:1534–47.

165. Stagnitti MN. Trends in prescribed outpatient opioid use and expenses in the U.S. civilian noninstitutionalized population, 2002–2012. Statistical Brief #478. Rockville, MD: Agency for Healthcare Research and Quality; 2015.

166. Gore M, Tai K-S, Sadosky A, Leslie D, Stacey BR. Use and costs of prescription medications and alternative treatments in patients with osteoarthritis and chronic low back pain in community-based settings. Pain Pract 2012;12:550–60.

167. Laffer A, Murphy R, Winegarden W, et al. An economic analysis of the costs and benefits associated with regular urine drug testing for chronic pain patients in the United States. Nashville, TN: Laffer Associates; 2011.

168. Chaparro L, Furlan A, Deshpande A, Mailis-Gagnon A, Atlas S, Turk D. Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review. Spine 2014;39:556–63.

169. Loder E, Weizenbaum E, Frishberg B, Silberstein S; American Headache Society Choosing Wisely Task Force. Choosing wisely in headache medicine: The American Headach Society's list of five things physicians and patients should question. Headache 2013;53:1651–9.

170. Gaskell H, Moore R, Derry S, Stannard C. Oxycodone for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2014; 2014 Jun 23;6:CD010692. doi: 10.1002/14651858.CD010692.pub2.

171. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med 2006;166:2087–93.

172. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev 2010; (1):CD006605 10.1002/14651858.CD006605.pub2.

173. Krebs EE, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. J Gen Intern Med 2009;24:733–8.

174. Ostelo RW, Deyo RA, Stratford P, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. Spine 2008;33:90–4.

175. Food and Drug Administration. Disposal of unused medicines: what you should know. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2015. Available at http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm186187.htm#Flush_List.

176. Food and Drug Administration. FDA blueprint for prescriber education for extended-release and long-acting opioid analgesics. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014.

177. Food and Drug Administration. Abuse-deterrent opioids: evaluation and labeling guidance for industry. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research; 2015.

DRAFT

178. Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain 2014;15:321–37.

179. Chu J, Farmer B, Ginsburg B, Hernandez S, Kenny J, Majlesi N. New York City emergency department discharge opioid prescribing guidelines. Queens, NY: New York City Department of Health and Mental Hygiene; 2013. Available at http://www.nyc.gov/html/doh/html/hcp/drug-opioid-guidelines.shtml.

180. Cheng D, Majlesi N. Clinical Practice Statement: Emergency department opioid prescribing guidelines for the treatment of non-cancer related pain. Milwaukee, WI: American Academy of Emergency Medicine; 2013.

181. Maryland Chapter, American College of Emergency Physicians. Maryland emergency department and acute care facility guidelines for prescribing opioids. Available at http://www.mdacep.org/MD%20ACEP%20Pamphlet%20FINAL_April%202014.pdf. 2014.

182. Paone D, Dowell D, Heller D. Preventing misuse of prescription opioid drugs. City Health Information 2011;30:23–30.

183. Thorson D, Biewen P, Bonte B, et al. Acute pain assessment and opioid prescribing protocol. Institute for Clinical Systems Improvement; 2014. Available at https://www.icsi.org/_asset/dyp5wm/Opioids.pdf.

184. American College of Emergency Physicians Opioid Guideline Writing Panel, Cantrill S, Brown MD, et al. Clinical policy: Critical issues in the prescribing of opioids for adult patients in the emergency department. Ann Emerg Med 2012;60:499–525.

185. Cost J, Delecoeuillerie G, Cohen de Lara A, LeParc JM, Paolaggi JB. Clinical course and prognostic factors in acute low back pain: an inception cohort study in primary care practice. BMJ 1994;308:577.

186. CDC. Common elements in guidelines for prescribing opioids for chronic pain. Atlanta, GA: US Department of Health and Human Services, CDC; 2015. Available at http://www.cdc.gov/drugoverdose/prescribing/common-elements.html.

187. Berlin D, Farmer BM, Rao RB, et al. Deaths and severe adverse events associated with anesthesia-assisted rapid opioid detoxification—New York City, 2012. MMWR Morb Mortal Wkly Rep 2013;62:777–80.

188. Berna C, Kulich RJ, Rathmell JP. Tapering long-term opioid therapy in chronic noncancer pain: Evidence and recommendations for everyday practice. Mayo Clin Proc 2015;90:828–42.

189. American College of Obstetricians and Gynecologists. Opioid abuse, dependence, and addiction in pregnancy. Committee Opinion No. 524. Obstet Gynecol 2012;119:1070–6.

190. National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic non-cancer pain; 2010. Available at http://nationalpaincentre.mcmaster.ca/opioid/documents.html.

191. Kroenke K, Spitzer RL, Williams JBBL. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. Gen Hosp Psychiatry 2010;32:345–59.

192. Saitz R, Cheng DM, Allensworth-Davies D, Winter MR, Smith PC. The ability of single screening questions for unhealthy alcohol and other drug use to identify substance dependence in primary care. J Stud Alcohol Drugs 2014;75:153–7.

193. Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. A single-question screening test for drug use in primary care. Arch Intern Med 2010;170:1155–60.

194. Yudko E, Lozhkina O, Fouts A. A comprehensive review of the psychometric properties of the Drug Abuse Screening Test. J Subst Abuse Treat 2007;32:189–98.

DRAFT

195. Reinert DF, Allen JP. The alcohol use disorders identification test: an update of research findings. Alcohol Clin Exp Res 2007;31:185–99.

196. Irvine JM, Hallvik SE, Hildebran C, Marino M, Beran T, Deyo RA. Who uses a prescription drug monitoring program and how? Insights from a statewide survey of Oregon clinicians. J Pain 2014;15:747–55.

197. Substance Abuse and Mental Health Services Administration. Clinical drug testing in primary care. Technical Assistance Publication (TAP) 32 HHS Publication No. (SMA) 12-4668. Rockville, MD: US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration; 2012.

198. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ 2015;350:h2698.

199. Paquin AM, Zimmerman K, Rudolph JL. Risk versus risk: a review of benzodiazepine reduction in older adults. Expert Opin Drug Saf 2014;13:919–34.

200. Schweizer E, Case WG, Rickels K. Benzodiazepine dependence and withdrawal in elderly patients. Am J Psychiatry 1989;146:529–31.

201. Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. JAMA Intern Med 2014;174:1947–54.

202. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiatry 2011;68:1238–46.

203. Jones CM, Campopiano M, Baldwin G, McCance-Katz E. National and state treatment need and capacity for opioid agonist medication-assisted treatment. Am J Public Health 2015;105:e55–63.

204. Mark T, Lubran R, McCance-Katz E, Chalk M, Richardson J. Medicaid coverage of medications to treat alcohol and opioid dependence. J Subst Abuse Treat 2015;55:1–5.

205. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev 2006; (1):CD001333.

206. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet 2011;377:1506–13.

207. Substance Abuse and Mental Health Services Administration. Physician waiver qualifications. Rockville, MD: US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration; 2015. Available at http://www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management.

208. American Society of Addiction Medicine. The ASAM national practice guideline for the use of medications in the treatment of addiction involving opioid use. Chevy Chase, MD: American Society of Addiction Medicine; 2015. Available at http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/national-practice-guideline.pdf?sfvrsn=22.

209. Reuben DB, Alvanzo AAH, Ashikaga T, et al. National Institutes of Health Pathways to Prevention Workshop: the role of opioids in the treatment of chronic pain. Ann Intern Med 2015;162:295–300.

DRAFT

BOX 1. CDC 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. Providers should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks to the patient.
2. Before starting opioid therapy for chronic pain, 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 if unsuccessful. Providers 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, providers should discuss with patients known risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy.

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

4. When starting opioid therapy for chronic pain, providers should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, providers should prescribe the lowest 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 dosage to ≥90 MME/day.
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 immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three of fewer days usually will be sufficient for most nontraumatic pain not related to major surgery.
7. Providers should evaluate benefits and harms with patients within 1–4 weeks of starting opioid therapy for chronic pain or of dose escalation. Providers 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, providers should work with patients to reduce opioid dosage and to discontinue opioids.

Assessing Risk and Addressing Harms of Opioid Use

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 dosage (≥50 MME) are present.
9. Providers 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 high opioid dosages or dangerous combinations that put him or her at high risk for overdose. Providers 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, providers 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.

DRAFT

11. Providers should avoid prescribing opioid pain medication for patients receiving benzodiazepines whenever possible.
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.

* 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); see full guideline for evidence ratings.

BOX 2. Interpretation of recommendation categories and evidence type

Recommendation Categories

Based on evidence type, balance between desirable and undesirable effects, values and preferences, and resource allocation (cost).

Category A recommendation: Applies to all persons; most patients should receive the recommended course of action.

Category B recommendation: Individual decision making needed; different choices will be appropriate for different patients. Providers help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.

Evidence Type

Based on study design as well as a function of limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, magnitude of treatment effects, dose-response gradient, and constellation of plausible biases that could change effects.

Type 1 evidence: Randomized controlled trials or overwhelming evidence from observational studies.

Type 2 evidence: Randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies.

Type 3 evidence: Observational studies or randomized controlled trials with notable limitations.

Type 4 evidence: Clinical experience and observations, observational studies with important limitations, or randomized controlled trials with several major limitations.

Steering Committee and Core Expert Group Members

Steering Committee: Deborah Dowell, MD, Tamara M. Haegerich, PhD; Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC; Roger Chou, MD; Oregon Health and Sciences University

Core Expert Group Members: Pam Archer, MPH, Oklahoma State Department of Health; Jane Ballantyne, MD; University of Washington (retired); Amy Bohnert, PhD; University of Michigan; Bonnie Burman, ScD; Ohio Department on Aging; Roger Chou, MD; Oregon Health and Sciences University; Phillip Coffin, MD, San Francisco Department of Public Health; Gary Franklin, MD, MPH; Washington State Department of Labor and Industries/University of Washington; Erin Krebs, MDH; Minneapolis VA Health Care System/University of Minnesota; Mitchel Mutter, MD, Tennessee Department of Health; Lewis Nelson, MD; New York University School of Medicine; Trupti Patel, MD, Arizona Department of Health Services; Christina A. Porucznik, PhD, University of Utah; Robert "Chuck" Rich, MD, FAAFP, American Academy of Family Physicians; Joanna Starrels, MD, Albert Einstein College of Medicine of Yeshiva University; Michael Steinman, MD, Society of General Internal Medicine; Thomas Tape, MD, American College of Physicians; Judith Turner, PhD, University of Washington

DRAFT

Roger Chou, MD assisted in the review of the scientific evidence and authorship of the guideline under a short-term detail through an Intergovernmental Personnel Act (IPA) appointment.

Core Expert Group (CEG) Disclosures

The experts disclose that they have no financial conflicts of interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. CDC reviewed content of disclosure statements to ensure that there is no bias. Experts disclose the following activities related to the content of this guideline: Pam Archer discloses authorship of the Oklahoma Emergency Department and Urgent Care Clinic Opioid Prescribing Guidelines and the Opioid Prescribing Guidelines for Oklahoma Health Care Providers in the Office Based Setting; Bonnie Burman discloses authorship of the Ohio Guidelines for Prescribing Opioids for the Treatment of Chronic, Non-Terminal Pain; Jane Ballantyne discloses that she has served as a paid consultant to Cohen Milstein Sellers & Toll, PLLC, and has special advisory committee responsibilities on the Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategies committee; Phillip Coffin discloses that in 2012 he provided expert testimony to the California State Assembly regarding a bill to expand naloxone access and reports that he is the principal investigator on a research study of methamphetamine dependence that receives donated injectable naltrexone from Alkermes, Inc.; Gary Franklin discloses authorship of the AMDG Interagency Guideline on Prescribing Opioids for Pain; Erin Krebs discloses that she represented the American College of Physicians at a 2014 Food and Drug Administration meeting on Abuse Deterrent Opioid Formulations; Lewis Nelson discloses his ad-hoc membership on the FDA Drug Safety and Risk Management Advisory Committee; Trupti Patel discloses authorship of the Arizona Opioid Prescribing Guidelines; Robert "Chuck" Rich discloses that he was an author of the 2013 American Academy of Family Physicians position paper on opioids and pain management; Joanna Starrels discloses that she received honoraria from the Betty Ford Institute; Thomas Tape discloses that he was an author of the 2013 American College of Physicians policy position paper on prescription drug abuse. CDC provided 100% of the funding for the supplemental evidence review tasks and meeting support. No foundation or industry support was accepted.

Stakeholder Review Group

John Markman, MD, American Academy of Neurology; Bob Twillman, PhD, American Academy of Pain Management; Edward C. Covington, MD, American Academy of Pain Medicine; Roger F. Suchyta, MD, FAAP, American Academy of Pediatrics; Kavitha V. Neerukonda, JD, American Academy of Physical Medicine and Rehabilitation; Mark Fleury, PhD, American Cancer Society Cancer Action Network; Penney Cowan, American Chronic Pain Association; David Juurlink, BPharm, MD, PhD, American College of Medical Toxicology; Gerald "Jerry" F. Joseph, Jr, MD, American College of Obstetrics and Gynecology; Bruce Ferrell, MD, AGSF, M. Carrington Reid, MD, PhD, American Geriatrics Society; Ashley Thompson, American Hospital Association; Barry D. Dickinson, PhD, American Medical Association; Gregory Terman MD, PhD, American Pain Society; Beth Haynes, MPPA, American Society of Addiction Medicine; Asokumar Buvanendran, MD, American Society of Anesthesiologists; Robert M. Plovnick; MD, American Society of Hematology; Sanford M. Silverman, MD, American Society of Interventional Pain Physicians; Andrew Kolodny, MD, Physicians for Responsible Opioid Prescribing.

The recommendations and all statements included in this guideline are those of CDC and do not necessarily represent the official position of any persons or organizations comprising the Stakeholder Review Group.

Peer Reviewers

Jeanmarie Perrone, MD, University of Pennsylvania; Matthew Bair, MD, Indiana University School of Medicine;, David Tauben, MD, University of Washington

DRAFT

TABLE. Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical evidence review ratings of the evidence for the key clinical questions regarding effectiveness and risks of long-term opioid therapy for chronic pain

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of evidence	Other factors	Estimates of effect/findings
Effectiveness and comparative effectiveness (KQ1)							
Effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (>1 year) outcomes							
Pain, function, and quality of life	None	—[†]	—	—	Insufficient	—	No evidence
Harms and adverse events (KQ2)							
Risks of opioids versus placebo or no opioids on opioid abuse, addiction, and related outcomes; overdose; and other harms							
Abuse or addiction	1 cohort study (n = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found long-term use of prescribed opioids associated with an increased risk of abuse or dependence diagnosis versus no opioid use (adjusted OR ranged from 14.9 to 122.5, depending on dose).
Abuse or addiction	10 uncontrolled studies (n = 3,780)	Very serious limitations	Very serious inconsistency	No imprecision	4	None identified	In primary care settings, prevalence of opioid abuse ranged from 0.6% to 8% and prevalence of dependence from 3% to 26%. In pain clinic settings, prevalence of misuse ranged from 8% to 16% and addiction from 2% to 14%. Prevalence of aberrant drug-related behaviors ranged from 6% to 37%.
Overdose	1 cohort study (n = 9,940)	Serious limitations	Unknown (1 study)	Serious imprecision	3	None identified	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) versus current nonuse.
Fractures	1 cohort study (n = 2,341) and 1 case–control study (n = 21,739 case patients)	Serious limitations	No inconsistency	No imprecision	3	None identified	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).
Myocardial infarction	1 cohort study (n = 426,124) and 1 case–control study (n = 11,693 case patients)	No limitations	No inconsistency	No imprecision	3	None identified	Current opioid use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95% CI = 1.19–1.37 and incidence rate ratio 2.66, 95% CI = 2.30–3.08).
Endocrinologic harms	1 cross-sectional study (n = 11,327)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI = 1.1–1.9).
How do harms vary depending on the opioid dose used?							

Abuse or addiction	1 cohort study (n = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared to no opioid prescription, the adjusted odds ratios were 15 (95% CI = 10–21) for 1 to 36 MME/day, 29 (95 % CI = 20–41) for 36 to120 MME/day, and 122 (95 % CI = 73–205) for ≥120 MME/day.
Overdose	1 cohort study (n = 9,940) and 1 case–control study (n = 593 case patients in primary analysis)	Serious limitations	No inconsistency	No imprecision	3	Magnitude of effect, dose response relationship	Versus 1 to 19 MME/day, one cohort study found an adjusted HR for an overdose event of 1.44 (95% CI = 0.57–3.62) for 20 to 49 MME/day that increased to 11.18 (95% CI = 4.80–26.03) at >100 MME/day; one case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI = 0.94–1.84) for 20 to 49 MME/day that increased to 2.88 (95% CI = 1.79–4.63) at ≥200 MME/day.
Fractures	1 cohort study (n = 2,341)	Serious limitations	Unknown (1 study)	Serious imprecision	3	None identified	Risk of fracture increased from an adjusted HR of 1.20 (95% CI = 0.92–1.56) at 1 to <20 MME/day to 2.00 (95% CI = 1.24–3.24) at ≥50 MME/day; the trend was of borderline statistical significance.
Myocardial infarction	1 cohort study (n = 426,124)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Relative to a cumulative dose of 0 to 1,350 MME during a 90-day period, the incidence rate ratio for myocardial infarction for 1350 to <2700 MME was 1.21 (95% CI = 1.02–1.45), for 2,700 to <8,100 MME was 1.42 (95% CI = 1.21–1.67), for 8,100 to <18,000 MME was 1.89 (95% CI = 1.54–2.33), and for >18,000 MME was 1.73 (95% CI = 1.32–2.26).
Motor vehicle crash injuries	1 case–control study (n = 5,300 case patients)	No limitations	Unknown (1 study)	No imprecision	3	None identified	No association between opioid dose and risk of motor vehicle crash injuries.
Endocrinologic harms	1 cross-sectional study (n = 11,327) New for update: 1 additional cross-sectional study (n=1,585)	Serious limitations	Consistent	No imprecision	3	None identified	Relative to 0 to <20 MME/day, the adjusted OR for ≥120 MME/day 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/day 1.16, 95% CI = 1.09–1.23), but the dose response was very weak among men receiving ER/LA opioids.

Dosing strategies (KQ3)							
Comparative effectiveness of different methods for initiating opioid therapy and titrating doses							
Pain	3 randomized trials (n = 93)	Serious limitations	Serious inconsistency	Very serious imprecision	4	None identified	Trials on effects of titration with immediate-release versus ER/LA opioids reported inconsistent results and had additional differences between treatment arms in dosing protocols (titrated versus fixed dosing) and doses of opioids used.
Overdose	New for update: 1 cohort study (n = 840,606)	Serious limitations	Unknown (1 study)	No imprecision	4	None identified	One new cross-sectional study found initiation of therapy with an ER/LA opioid associated with increased risk of overdose versus initiation with an immediate-release opioid (adjusted HR 2.33, 95% CI = 1.26–4.32).
Comparative effectiveness of different ER/LA opioids							
Pain and function	3 randomized trials (n = 1,850)	Serious limitations	No inconsistency	No imprecision	3	None identified	No differences
All-cause mortality	1 cohort study (n = 108,492) New for update: 1 cohort study (n = 38,756)	Serious limitations	Serious inconsistency	No imprecision	4	None identified	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) and 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).
Abuse and related outcomes	1 cohort study (n = 5,684)	Serious limitations	Unknown (1 study)	Serious imprecision	4	None identified	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.
Long- versus immediate-release opioids							
Endocrinologic harms	New for update: 1 cross-sectional study (n = 1,585)	Serious limitations	Unknown (1 study)	No imprecision	4	None identified	One cross-sectional study found ER/LA opioids associated with increased risk of androgen deficiency versus immediate-release opioids (adjusted OR 3.39, 95% CI = 2.39–4.77).
Dose escalation versus dose maintenance or use of dose thresholds							
Pain, function, or withdrawal due to opioid misuse	1 randomized trial (n = 140)	Serious limitations	Unknown (1 study)	Very serious imprecision	3	None identified	No difference between more liberal dose escalation versus maintenance of current doses in pain, function, or risk of withdrawal due to opioid misuse, but there was limited separation in opioid doses between groups (52 versus 40 MME/day at the end of the trial).

DRAFT

Immediate-release versus ER/LA opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled and continuous versus as-needed dosing of opioids; or opioid rotation versus maintenance of current therapy							
Pain, function, quality of life, and outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effects of decreasing or tapering opioid doses versus continuation of opioid therapy							
Pain and function	1 randomized trial (n = 10)	Very serious limitations	Unknown (1 study)	Very serious imprecision	4	None identified	Abrupt cessation of morphine was associated with increased pain and decreased function compared with continuation of morphine.
Comparative effectiveness of different tapering protocols and strategies							
Opioid abstinence	2 nonrandomized trials (n = 150)	Very serious limitations	No inconsistency	Very serious imprecision	4	None identified	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3–6 months
Risk assessment and risk mitigation strategies (KQ4)							
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							
Opioid risk tool	3 studies of diagnostic accuracy (n = 496) New for update:2 studies of diagnostic accuracy (n = 320)	Serious limitations	Very serious inconsistency	Serious imprecision	4	None identified	Based on a cutoff score of >4 (or unspecified), five studies (two fair-quality, three poor-quality) reported sensitivity that ranged from 0.20 to 0.99 and specificity that ranged from 0.16 to 0.88).
Screener and Opioid Assessment for Patients with Pain, Version 1	2 studies of diagnostic accuracy (n = 203)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity was 0.38 in one study, for a positive likelihood ratio of 1.11 and a negative likelihood ratio of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in one study.
Screener and Opioid Assessment for Patients with Pain-Revised	New for update: 2 studies of diagnostic accuracy (n = 320)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a cutoff score of >3 or unspecified, sensitivity was 0.25 and 0.53 and specificity was 0.62 and 0.73 in two studies, for likelihood ratios close to 1.
Brief Risk Interview	New for update: 2 studies of diagnostic accuracy (n = 320)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a "high risk" assessment, sensitivity was 0.73 and 0.83 and specificity was 0.43 and 0.88 in two studies, for positive likelihood ratios of 1.28 and 7.18 and negative likelihood ratios of 0.63 and 0.19.
Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
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							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain							
Outcomes related to abuse	None	–	–	–	Insufficient	–	No evidence

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							
Outcomes related to abuse	None	–	–	–	Insufficient	–	No evidence
Comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids							
Outcomes related to abuse	None	–	–	–	Insufficient	–	No evidence
Effects of opioid therapy for acute pain on long-term use (KQ5)							
Long-term opioid use	New for update: 2 cohort studies (*n* = 399,852)	Serious limitations	No inconsistency	No imprecision	3	None identified	One study found use of opioids within 7 days of low-risk surgery associated with increased likelihood of opioid use at 1 year (adjusted OR 1.44, 95% CI = 1.39–1.50), and one study found use of opioids within 15 days of onset of low back pain among workers with a compensation claim associated with increased risk of late opioid use (adjusted OR 2.08, 95% CI = 1.55–2.78 for 1 to 140 MME/day and OR 6.14, 95% CI = 4.92–7.66 for ≥450 MME/day).

Abbreviations: CI = confidence interval; HR = hazard ratio; MME = morphine milligram equivalents; OR = odds ratio.

*Ratings were made per GRADE quality assessment criteria; "no limitations" indicates that limitations assessed through the GRADE method were not identified.

†Not applicable as no evidence was available for rating

Appendix 1 online only

Appendix 2 online only

DRAFT