CDC Guideline for Prescribing Opioids for Chronic Pain, 2016

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Summary

This guideline provides recommendations for primary care providers who are prescribing opioids for chronic pain outside of end-of-life care. The guideline addresses (1) when to initiate or continue opioids for chronic pain outside of end-of-life care; (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, basing recommendations on a systematic review of the scientific evidence, while considering benefits and harms, values and preferences, and resource implications. CDC consulted with experts knowledgeable in the areas of opioid prescribing, addiction, substance use disorder treatment, and pain management to inform the recommendations, and provided opportunities for stakeholder review and public engagement. It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. These recommendations are intended to promote safer use of opioids to improve clinical practice, patient outcomes, and public health.

Introduction

Background and Objective

Opioids are commonly prescribed for pain. An estimated 20% of patients presenting to physician offices with pain symptoms or diagnoses receive an opioid prescription (1). In 2012, health care providers wrote 259 million prescriptions for opioid pain medication – enough for every American adult to have a bottle of pills (2). Opioid prescriptions per capita increased 7.3% from 2007 to 2012, with prescribing rates for family practice, general practice, and internal medicine increasing more than the average opioid rate of growth (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 on how to use opioid pain medication (2).

Prevention, assessment, and treatment of chronic pain is a challenge for health providers and systems (4). It is important that patients receive appropriate pain treatment based on a careful consideration of the benefits and risks of treatment options. The number of people experiencing chronic pain in the United States is substantial. Chronic pain has been variously defined but is considered within this guideline as pain that typically lasts longer than 3 months or past the time of normal tissue healing (5). Chronic pain can be the result of an underlying medical disease or condition, an injury, medical treatment, inflammation, or unknown cause (4). Estimates of the prevalence of chronic pain vary. The 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, frequent severe headaches) is estimated at 43% among adults in the United States (7). Most recently, analysis of data from the 2012 National Health Interview Study revealed an estimated prevalence of daily (chronic) pain of 11.2% (8). Yet, the presence of a significant proportion of individuals with chronic pain or painful conditions does not imply that opioid pain medications are the optimal course of treatment for all these

individuals. The number of people who could potentially benefit from opioid pain medication long term is difficult to estimate. Although evidence supports short-term efficacy of opioids for reducing non-cancer nociceptive and neuropathic pain lasting < 16 weeks (9), there is a lack of studies on long-term benefits of opioids for chronic pain (pain lasting > 3 months) with outcomes examined at least 1 year later (10). Based on recent data available from health systems, it is estimated that 9.6 to 11.5 million adults, or approximately 3-4% of the adult US population, are prescribed long-term (chronic) opioid therapy (11).

Unfortunately, there are serious risks of opioid pain medication use, including opioid use disorder (opioid dependence or abuse) and overdose. In 2013, more than 16,000 persons died from overdose related to opioid pain medication in the United States, four times the number who died from overdoses related to these drugs in 1999 (12). Sales of opioid pain medication have increased in parallel with overdose deaths (13). In 2013, an estimated 1.9 million persons abused or were dependent on prescription opioid pain medication (14). Having a history of an opioid prescription is one of many factors that increase risk for overdose and opioid use disorder (15-17), suggesting the importance of guidance on safer prescribing practices for providers.

The objective of this guideline is to provide new 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 end-of-life care (e.g., hospice care). While the guideline does not focus broadly on pain management, appropriate use of long-term opioid therapy must be considered within the context of pain management strategies (including non-opioid pain medications and non-pharmacologic treatments). The guideline outlines strategies for safer use of opioid pain medication for chronic pain. Recommendations are based on a systematic review of the best available evidence, with consultation from an expert panel. Improving the way opioid pain medications are prescribed for chronic pain through clinical practice guidelines is intended to ensure patients have access to safer, more effective treatment while reducing the number of persons who develop opioid use disorder, overdose, or experience adverse events related to these drugs.

Rationale

Primary care providers report concern about opioid pain medication misuse, find managing patients with chronic pain stressful, express worry about patient addiction, and report insufficient training in prescribing opioids (18). Across specialties, physicians agree that while opioid pain medication can be effective in controlling pain, physical dependence, tolerance, and addiction are consequences of prolonged use; long-term opioid therapy is often overprescribed for patients with chronic non-cancer pain; and overprescribing will decrease the effectiveness of the medication in relieving pain (19). These attitudes and beliefs combined with increasing trends in opioid use disorder and overdose associated with opioid pain medication underscore the need for better provider guidance on opioid prescribing. Clinical practice guidelines focused on prescribing can improve provider knowledge, change prescribing practices, (20) and ultimately benefit patient health.

Professional organizations, states, and federal agencies have developed guidelines on opioid prescribing (e.g., the American Pain Society/American Academy of Pain Medicine, 2009; Washington Agency Medical Directors Group, 2015; and the US Department of Veteran Affairs/Department of Defense, 2010). (21-23). There are some common elements across existing guidelines, including dosing thresholds, cautious titration, and risk mitigation strategies such as risk assessment tools, treatment agreements, and urine drug testing. However, there is considerable variability in the specific recommendations (e.g., dosing threshold of 90 morphine milligram equivalents (MME)/day versus 200 MME/day), audience (e.g., primary care versus specialists), use of evidence (e.g., systematic review versus expert opinion), and rigor of methods for addressing conflict of interest (see Nuckols et al. for a review (24)). Most guidelines, especially those that are not based on scientific studies published in 2010 or later, also do not reflect the most recent scientific evidence about risks related to opioid dosage.

New CDC guidelines can offer clarity on recommendations based on the most recent scientific evidence. Development of clinical practice guidelines with public funding decreases the likelihood of conflicts of interest

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that can result in commercial influence and bias. CDC has a unique role in providing to healthcare professionals data and evidence-based guidance and tools that can improve both clinical and public health practice. 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, extended-release/long-acting (ER/LA) opioids for acute pain) (17, 25, 26). Addressing problematic prescribing through guidelines has the potential to result in optimization of care and improvements in patient safety based on evidence-based practice (20), as well as potentially disrupt the cycle of opioid pain medication misuse and abuse that contribute to the overdose epidemic. Because of CDC's reach, CDC recommendations for primary care practitioners can be efficiently translated and disseminated for rapid adoption into practice.

Scope and Audience

This guideline is intended for primary care providers (e.g. family physicians, internists) who are treating patients for chronic pain in outpatient settings. Primary care providers account for nearly half of all dispensed opioid prescriptions and have experienced above-average growth in prescribing rates (3). This guideline is intended to apply to patients aged ≥ 18 years with chronic pain (i.e., pain lasting longer than 3 months or past the time of normal tissue healing) outside of end-of-life care (e.g., hospice care). The guideline is not intended for 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 palliative care. Patients include those with chronic pain, regardless of whether they have a current or previous diagnosis of cancer. Use of opioid pain medication with special populations (e.g. older adults, pregnant women) and in populations with conditions posing special risks (e.g., substance use disorder) is addressed within the recommendations.

The recommendations are not intended for guiding use of opioid pain medication as part of medication-assisted treatment for substance use disorders. Some of the recommendations might be relevant for acute care settings, but use in these settings is not the focus of this guideline. Readers are referred to other sources for prescribing recommendations within these settings, such as the American College of Emergency Physicians' guideline for prescribing of opioids in the emergency department, the American Society of Anesthesiologists' guideline for acute pain management in the perioperative setting, and the Washington Agency Medical Directors' Group Interagency Guideline on Prescribing Opioids for Pain, Part II: Prescribing Opioids in the Acute and Subacute Phase (23, 27, 28). In addition, management of acute pain emergencies associated with chronic conditions such as vaso-occlusive crisis in sickle cell disease is not a focus of this guideline. 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 painful complications of sickle cell disease (29).

Guideline Development Methods

Guideline Development Using GRADE

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 grades the overall quality of each body of evidence as high, moderate, low, or very low. Studies using randomized designs are initially rated as high quality, and observational studies are rated as low quality. Quality ratings change 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. The method grades recommendations as strong or weak. Four major factors determine the strength of recommendations: the quality of evidence, the balance between desirable and undesirable effects, values and preferences, and costs. Strong recommendations indicate that most patients should receive the recommended course of action and the recommendation could be adopted as policy in most situations. Weak recommendations indicate that different choices will be appropriate for different patients, such that providers must help patients arrive at a decision

consistent with patient values, preferences, and specific clinical situations; policy making often requires substantial debate and stakeholder involvement (30). For an extensive discussion of GRADE methodology, see the six-part BMJ journal series (30) or the twenty-part Journal of Clinical Epidemiology series on the approach to systematic review and guideline development (31).

A previously published Agency for Healthcare Research and Quality (AHRQ)-sponsored systematic review on *The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain* (10, 32) served as an initial foundation 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 effort, 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 the Clinical Evidence Review section below and Online Appendix 1 for more detail). CDC developed GRADE evidence tables to illustrate the strength of the evidence for each clinical question.

As identified in the AHRQ-sponsored clinical evidence review, the evidence base regarding the effectiveness and risks of long-term opioid treatment is rated as low in quality. 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 cost efficiency 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, focusing on the following four areas: effectiveness of alternative treatments (i.e., non-pharmacologic and non-opioid 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, and risk stratification/mitigation approaches); provider and patient values and preferences; and resource implications. CDC constructed narrative summaries of this contextual evidence and used the information to support the clinical recommendations (see the Contextual Evidence Review section below and Online Appendix 2 for more detail).

Based on a review of the clinical and contextual evidence (review methods described in more detail below), CDC drafted recommendation statements focusing on determining when to initiate or continue opioids for chronic pain outside of end-of-life care; 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 inform a refinement of the recommendations.

Solicitation of Expert Opinion

CDC recruited a Core Expert Group (CEG) to assist in interpreting the evidence and translating the evidence into recommendations. Group members provided individual consultation and were not part of a designated Federal Advisory Committee. The CEG consisted of subject matter experts, primary care professional society representatives, state agency representatives, and an expert in guideline development methodology (see Appendix A for a list of CEG members). CDC identified subject matter experts with high scientific standing; appropriate academic training and relevant 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 target audience for this guideline. Finally, CDC identified state agency 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. In selecting members, CDC aimed to minimize conflict of interest, enhance objective assessment of the evidence, and reduce bias.

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For a guideline to be credible, it is important to eliminate or effectively manage sources of bias. These sources of bias might include financial relationships with industry, intellectual preconceptions, and previously stated public positions. Prior to participation, CDC asked CEG members to reveal potential conflicts of interest. Members could not serve if they held conflicts that could be anticipated to have a direct and predictable effect on the recommendations. CDC excluded persons with conflicts of interest from the CEG, particularly persons with a financial or promotional relationship with a company that makes a product that might be affected by the guideline (e.g., conflicts related to employment and consulting, research support, and financial investments). CDC reviewed potential non-financial 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. Thus, all CEG members 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 in Appendix B.

The CEG reviewed summaries of the scientific evidence and CDC's draft recommendation statements. CEG members provided individual ratings for each draft recommendation statement based on the balance of benefits and risks, evidence strength, certainty of values and preferences, cost, recommendation strength, rationale, importance, clarity, and ease of implementation. CDC convened CEG members at an in-person meeting June 23-24, 2015 in Atlanta, GA to discuss the evidence and recommendations and obtain expert opinions. The CEG provided individual opinions at the meeting within a group discussion; no formal voting consensus processes were used. At the meeting, CDC noted CEG members' comments and any dissenting opinions on the recommendations. CEG members also reviewed the final guideline document and provided written comments for consideration by CDC.

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 federal partners to observe the CEG meeting and provide comment on the recommendations after the meeting. Interagency collaboration will be critical for translation of these recommendations into clinical practice. Federal partners included representatives from the Substance Abuse and Mental Health Services Administration, National Institute on Drug Abuse, FDA, US Department of Veterans Affairs, US Department of Defense, Office of the National Coordinator for Health Information Technology, Centers for Medicare and Medicaid Services, National Institute of Occupational Safety and Health, 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 specificity, applicability, and implementability of the recommendations. The SRG included representatives from professional organizations that represent specialties that commonly prescribe opioids (e.g., pain medicine, physical medicine and rehabilitation) as well as delivery systems within which opioid prescribing occurs (e.g., hospitals). The group also included representation from community organizations with interests in pain management and opioid prescribing. For a full list of the SRG members, see Appendix C. CDC identified representatives from each of the SRG organizations and provided a copy of the guideline for comment. Once input is received by the full SRG, CDC will review comments and make revisions to the guideline prior to finalization.

Peer Review

Peer review requirements applied to this guideline because they provide influential scientific information that could have a clear and substantial impact on public and private sector decisions. Three experts will independently peer review the guideline to determine the reasonableness of recommendations and ensure that scientific

uncertainties are clearly identified. CDC selected peer reviewers based on expertise and diversity of scientific viewpoints, while addressing conflict of interest concerns and ensuring independence from the guideline development process. CDC placed the names of peer reviewers on the CDC and the National Center for Injury Prevention and Control Peer Review Agenda. CDC will review peer reviewer comments and will revise the guideline prior to finalization.

Public Engagement

To obtain perspectives from the public, including providers and prospective patients, CDC will convene a public engagement webinar and circulated information about the webinar in advance through announcements to partners. CDC will host the webinar on September 16, 2015 and will provide information about the methodology for developing the guideline and present the key recommendations. CDC will solicit comments during this open forum and will revise the guideline in response.

Clinical Evidence Review

Primary Clinical Questions

For this guideline, CDC addressed five primary clinical questions regarding the effectiveness, benefits, and harms of opioids for chronic pain through systematic reviews of the scientific evidence. A previously published AHRQ-funded systematic review on the effectiveness and risks of long-term opioid treatment of chronic pain comprehensively addressed four clinical questions (10, 32). 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 and in collaboration with a methodologist conducted a systematic review of the scientific evidence to address it. In brief, the five clinical questions addressed:

1. The effectiveness of long-term opioid therapy versus placebo, no opioid therapy, or non-opioid 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);

2. 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);

3. The comparative effectiveness of opioid dosing strategies (different methods for initiating and titrating opioids; short-acting versus ER/LA opioids; different ER/LA opioids; short-acting 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);

4. The accuracy of instruments for predicting risk of 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 of opioid overdose, addiction, abuse, or misuse; and the comparative effectiveness of treatment strategies for managing patients with addiction (KQ4); and

5. The effects of prescribing opioid therapy versus not prescribing opioid therapy for acute pain on long-term use (KQ5).

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A detailed listing of the key questions can be found in Online Appendix 1.

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, 32). Study authors developed the protocol using a standardized process (33) with input from experts and the public and registered the protocol in the PROSPERO database (34). 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.

Summary of Findings for Clinical Questions

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 of serious harms that appears to be dose-dependent.

The Table shows the GRADE evidence summary with levels of evidence ratings for the five clinical questions. This summary is based on studies included in the AHRQ 2014 review (35 studies) plus additional studies identified in the updated search (seven studies). Additional details on findings from the original review are available in the full 2014 AHRQ report (10, 32). Full details on the clinical evidence review findings supporting this guideline can be found in Online Appendix 1.

Effectiveness

For KQ1, no study of opioid therapy versus placebo, no opioid therapy, or non-opioid therapy for chronic pain evaluated long-term (>1 year) outcomes related to pain, function, or quality of life. Most placebo-controlled randomized trials were ≤ 6 weeks in duration. Thus, the quality of evidence for KQ1 is very low (0 studies contributing) (10).

Harms

For KQ2, the quality of evidence is low (12 studies contributing; 11 from the original review plus one new study). One fair-quality cohort study found long-term opioid therapy is associated with increased risk of an opioid abuse or dependence diagnosis versus no opioid prescription (15). Rates of opioid abuse or dependence ranged from 0.7% with low-dose chronic therapy to 6.1% with high-dose chronic therapy, versus 0.004% with no opioids. Ten fair-quality uncontrolled studies reported estimates of opioid abuse, addiction, and related outcomes (35-45). In primary care settings, prevalence of opioid dependence (using DSM-IV criteria) ranged from 3% to 26% (35, 36, 39). In pain clinic settings, prevalence of addiction ranged from 2% to 14% (37, 38, 40, 41, 43-45).

Factors associated with increased risk of misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications (36, 42). Two studies reported on the association between opioid use and risk of overdose (46, 47). One large, fair-quality retrospective cohort study found recent opioid use was associated with increased risk of any overdose events and serious overdose events versus non-use (46). It also found higher doses associated with increased risk. Relative to 1 to 19 MME/day, the adjusted hazard ratio (HR) for an overdose was 1.44 for 20 to 49 MME/day, 3.73 for 50 to 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 of overdose (47). Relative to 1 to 19 MME/day, the adjusted odds ratio (OR) was 1.32 for 20 to 49 MME/day, 1.92 for 50 to 99 MME/day, 2.04 for 100 to 199 MME/day, and 2.88 for ≥200 MME/day.

Findings of increased fracture risk for current opioid use, versus non-use, were mixed in two studies (48, 49). Two studies found an association between opioid use and increased risk of cardiovascular events (50, 51). 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 new newly reviewed study) (52, 53). One study found opioid dosages ≥20 MME/day associated with increased odds of road trauma among drivers (54).

Opioid Dosing Strategies

For KQ3, the quality of evidence is very low (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 short-acting opioids for titrating patients to stable pain control (55, 56). One new fair-quality cohort study of Veterans Affairs patients found initiation of therapy with an ER/LA opioid associated with greater risk of nonfatal overdose than initiation with a short-acting opioid, with risk greatest in the first 2 weeks after initiation of treatment (57).

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 (58-60), but had methodological shortcomings. A fair-quality retrospective cohort study based on national Veterans Affairs system pharmacy data found methadone associated with lower overall risk of all-cause mortality versus morphine (61) and a fair-quality retrospective cohort study based on Oregon Medicaid data found no statistically significant differences between methadone versus long-acting morphine in risk of death or overdose symptoms (62). However, a new observational study (63) found methadone associated with increased risk of 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 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 versus maintenance of current doses after 12 months in pain, function, all-cause withdrawals, or withdrawals due to opioid misuse (64). 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 short-acting opioids; short-acting 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 (65-67).

Risk Assessment and Mitigation

For KQ4, the quality of evidence is low or very low (six studies contributing; four from the original review plus two new studies). The 2014 AHRQ report included four studies (68-71) 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) (69-71) were extremely inconsistent; evidence for other risk assessment instruments was very sparse, and studies had serious methodological shortcomings. One additional fair-quality (72) and one poor-quality (73) 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 non-informative (positive likelihood ratio close to 1) to moderately useful (positive likelihood ratio >5). The SOAPP-R was associated with non-informative likelihood ratios (estimates close to 1) in both studies.

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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 quality of evidence is low (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 (74). Use of opioids within 7 days of surgery was associated with increased risk of use at 1 year. The other study found early opioid use (defined as use within 15 days following onset of pain) among patients with a workers' compensation claim for acute low back pain associated with an increased likelihood of receiving five or more opioid prescriptions 30 to 730 days following onset versus non-use that increased with greater early exposure (75).

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 non-pharmacologic (e.g., cognitive behavioral therapy [CBT], exercise therapy, interventional treatments, multimodal pain treatment) and non-opioid pharmacologic treatments (e.g., acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], antidepressants, anticonvulsants);
- 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;
- Provider and patient values and preferences related to opioids and medication risks, benefits, and use; and
- Resource implications 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; guidelines with recommendations related to specific provider actions such as urine drug testing or opioid tapering protocols).

Contextual Evidence Review Methods

CDC conducted "rapid reviews" of the contextual evidence on alternative treatments, benefits and harms, values and preferences, and resource implications. Rapid reviews are used when there is a need to streamline the systematic review process to obtain evidence in a short time frame (76). Methods used to streamline the process include limiting searches by databases, years, and languages considered, and truncating quality assessment and data abstraction protocols. Given the public health urgency of developing opioid prescribing recommendations, a rapid review was required for the current guideline.

Detailed information about contextual evidence data sources and searches, inclusion criteria, study selection, and data extraction and synthesis are available in Online Appendix 2. 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 was not systematically searched. Database sources varied by topic, including MEDLINE,

PsycINFO, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. Multiple reviewers scanned study abstracts identified through the database searches, and abstracted relevant studies for review. CDC constructed narrative summaries and tables based on relevant articles that met inclusion criteria.

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. The studies that addressed benefits and harms, values and preferences, and resource implications 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.

Summary of Findings for Contextual Areas

Readers will find full narrative reviews and tables that summarize key findings from the contextual evidence review in Online Appendix 2.

Effectiveness of Alternative Treatments

Several non-pharmacologic and non-opioid pharmacologic treatments have been shown to be effective in managing chronic pain. For example, cognitive-behavioral therapy (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 catastrophizing (77). Exercise therapy can improve pain and function in chronic low back pain (78), improve function and reduce pain in osteoarthritis of the knee (79) and hip (80), and improve well-being, fibromyalgia symptoms, and physical function in fibromyalgia (81). Multimodal integrative therapies (e.g., therapies that pair relaxation approaches with CBT or exercise) can sometimes have more positive effects than single modalities (82). Non-opioid 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 NSAIDs as first-line pharmacotherapy for osteoarthritis (83-88) or for low back pain (89); however, NSAIDs and COX-2 inhibitors do have gastrointestinal, renal, and cardiovascular risks. The FDA has recently strengthened existing label warnings that NSAIDs increase risks for heart attack and stroke, including that these risks may increase with longer use or at higher doses (90). Several guidelines agree that first and second-line drugs for neuropathic pain include anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, and SNRIs (91-94). 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. 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 (95).

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/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 are presented in the background section of this document, with detailed information presented in Online Appendix 2.

Regarding specific opioids and formulations, as noted by the U.S. Food and Drug Administration, 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 and for which alternative treatment options are inadequate (96). Time-scheduled opioid use was associated with substantially higher average daily opioid

dosage than as-needed opioid use in one study (97). 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 in states that participated in the Drug Abuse Warning Network, despite representing < 2% of opioid prescriptions outside of opioid treatment programs in the United States (98).

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 (16, 17, 99-101). 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 (16, 17) as well as the two studies in the clinical evidence review (102, 103) 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 non-malignant pain was between 1.3 (103) and 1.9 (17) for dosages of 20 to less than 50 MME/day, between 1.9 (103) and 4.6 (17) for dosages of 50 to less than 100 MME/day, and between 2.0 (103) and 8.9 (102) for dosages of at least 100 MME/day. A recent study of Veterans Health Administration patients with chronic pain (103) 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). 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 (104).

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 (103-105). In one of these studies (103), 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.

Regarding duration of use, patients can experience tolerance and loss of effectiveness of opioids over time (106). Patients who do not experience clinically meaningful pain relief early in treatment (e.g., within 1 month) are unlikely to experience pain relief with longer term use (107).

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 due to the types of study designs and methods employed, and there is not clear consensus regarding development of obstructive sleep apnea syndrome (108). 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 (109), 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) (22). Reduced renal and/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 (110). Age-related changes in patients ≥ 65 years such as reduced renal function and medication clearance, even in the absence of renal disease (111), 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 fracture related to opioids (112-114). 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 (neural tube defects (115, 116) congenital heart defects (116), and gastroschisis (116)), pre-term delivery (117), poor fetal growth (117), stillbirth (117), and neonatal abstinence syndrome (118). Patients with mental health co-morbidities and patients with histories of substance use disorders might be at higher risk than other patients for opioid use disorder (119-121). Recent analyses found that depressed patients were at higher risk for drug overdose than patients without depression,

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particularly at higher opioid dosages, although investigators were unable to distinguish unintentional overdose from suicide attempts (122). In case-control and case-cohort studies, frequency of substance abuse/dependence was more prevalent among patients experiencing overdose than among patients not experiencing overdose (12% versus 6% (102), 40% versus 10% (17), 26% versus 9% (16)).

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 (99, 123)) that are available to prescribers in the PDMP (99). However, limited evaluation of PDMPs at the state level has revealed mixed effects on changes in prescribing and mortality outcomes (20). 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.

Finally, regarding 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 of opioid overdose death at the community level (124).

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 (125), or interference with appropriate pain treatment (126). With the exception of a study noting an association between abuse-deterrent OxyContin formulation and heroin use, showing that some patients in qualitative interviews reported switching to another opioid including heroin (127), CDC did not identify studies evaluating these potential outcomes.

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 (128), to predict (129) or detect (130) prescription drug abuse, and to discuss abuse with their patients (130). Although providers have reported favorable beliefs and attitudes about improvements in pain and quality of life attributed to opioids (131) 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%). Majorities have reported adverse events including tolerance (62%) and physical dependence (56%) occurring often among patients. Providers do not consistently use practices intended to decrease the risk of misuse, such as PDMPs (132, 133) urine drug testing (134), and opioid treatment agreements (135). 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 EHR systems) (136), 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 (137).

Many patients do not have an opinion about “opioids,” or know what this term means (138). Most are familiar with “narcotics.” About a third associated “narcotics” with addiction or abuse, and about half feared “addiction” from long-term “narcotic” use (138). Most patients taking opioids experience side effects (73% of patients taking hydrocodone for non-cancer pain (139), 96% of patients taking opioids for chronic pain (140)), and side effects, rather than pain relief, have been found to explain most of the variation in patients’ preferences related to taking opioids (140). For example, patients taking hydrocodone for non-cancer pain commonly reported side effects including dizziness, headache, fatigue, drowsiness, nausea, vomiting, and constipation (139). Chronic pain patients in focus groups emphasized effectiveness of goal setting for increasing motivation and functioning (141).

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Patients taking high dosages report reliance on opioids despite ambivalence about their benefits (142) and regardless of pain reduction, report problems, concerns, side effects, or perceived helpfulness (143).

Resource Implications

Cost is an important consideration in understanding the feasibility of clinical recommendations. CDC searched for evidence on opioid therapy compared to 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 non-medical use of prescription opioids (144), $55.7 billion for abuse, dependence, and misuse of prescription opioids (145), and $20.4 billion for direct and indirect costs related to opioid-related overdose alone (146). Although there are perceptions that opioid therapy for chronic pain is less expensive than more time-intensive non-pharmacologic 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 (147). COX-2 inhibitors, SNRIs, anticonvulsants, topical analgesics, physical therapy, and CBT are also associated with lower median annual costs compared with opioid therapy (10). 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 between $211 and $363 per test (148).

Recommendations

The recommendations are categorized into three areas for consideration:

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

There are 12 recommendations. Each recommendation is followed by a rationale for the recommendation, with considerations for implementation noted. In accordance with the GRADE process, CDC based the recommendations on consideration of the clinical evidence, contextual evidence (including benefits and harms, values and preferences, resource implications), and expert opinion. For each recommendation statement, CDC notes the strength of the recommendation (strong or weak) and the strength of the evidence (high, moderate, low, very low) supporting the statement. Experts from the Core Expert Group ("experts") expressed support for all 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.

Determining When to Initiate or Continue Opioids for Chronic Pain Outside of End-of-Life Care

1. **Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Providers should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks** (strong recommendation, low quality of evidence).

   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, and the clinical evidence review found insufficient evidence to determine whether pain relief is sustained or whether function or quality of life improves with long-term use of opioids (KQ1). While benefits in pain, function, and quality of life with long-term opioid use for chronic pain are uncertain, risks of 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 of 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 from opioid pain medication-related overdoses every year (contextual evidence review).

Based on contextual evidence, many non-pharmacologic therapies, including exercise therapy, weight loss, and psychological therapies such as CBT can ameliorate chronic pain. In particular, exercise therapy and CBT are activating therapies that address psychosocial contributors to pain and improve function. Several non-opioid 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, and antidepressants such as tricyclics and SNRIs as well as selected anticonvulsants are effective in neuropathic pain conditions and in fibromyalgia (contextual evidence review). Non-opioid pharmacologic therapies are associated with some risks, particularly in older patients, pregnant patients, and patients with certain co-morbidities such as cardiovascular, renal, and liver disease (contextual evidence review). However, these therapies are not associated with drug dependence, and the numbers of fatal overdoses associated with the non-opioid medications studied are a fraction of those associated with opioid medications (contextual evidence review).

Given uncertain benefits and substantial risks, experts agreed that opioids should not be considered first-line or routine therapy for chronic pain outside of end-of-life care. Non-pharmacologic therapy including exercise therapy and CBT should be used to reduce pain and improve function in patients with chronic pain. If pharmacologic therapy is needed, non-pharmacologic therapy should be used in combination with non-opioid pharmacologic therapy to reduce pain and improve function.

2. **Before starting long-term opioid therapy, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety** (strong recommendation, very low quality of evidence).

The clinical evidence review found insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and found an increased risk of 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 with inconsistent results (KQ4). These findings suggest it is very difficult for providers to predict whether benefits of opioids for chronic pain will outweigh risks of ongoing treatment for individual patients.

Experts agreed that before opioid therapy is initiated for chronic pain outside of end-of-life care, providers should determine how effectiveness will be evaluated and should establish treatment goals with patients. While 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, if opioids are no longer needed, or if adverse events put the patient at risk), to improve patient safety. 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 (149) to track patient outcomes. Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function (150). Monitoring progress toward patient-centered functional goals (e.g., walking the dog or walking around the block, returning to part-time work, attending kids' games) can also contribute to the assessment of functional improvement. If patients on long-term opioid therapy 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 non-pharmacologic and non-opioid pharmacologic approaches to pain management (see Recommendation 1).

3. **Before starting and periodically during opioid therapy, providers should discuss with patients risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy** (strong recommendation, low quality of evidence).

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 is 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:

- Be explicit and realistic about expected benefits of opioids, explaining that there is not good evidence that opioids improve 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 common adverse effects of opioids such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opioids as well as more serious adverse effects of opioids including development of a potentially serious lifelong opioid use disorder and potentially fatal overdose.
- 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 and not more opioids or more often.
- Review increased risks of overdose when opioids are taken with benzodiazepines, other sedatives, alcohol, illicit drugs such as heroin, or other opioids.
- Discuss the importance of periodic re-assessment 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).
- Discuss risks to family members and individuals in the community if opioids are intentionally or unintentionally shared with others for whom they are not prescribed, including the possibility that others may experience overdose at the same or at lower dosage than prescribed for the patient. Discuss storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids (151).

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).

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

4. **When starting opioid therapy, providers should prescribe short-acting opioids instead of extended-release/long-acting (ER/LA) opioids** (strong recommendation, very low quality of evidence).

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 of overdose among patients initiating treatment with ER/LA opioids than among those initiating treatment with short-acting opioids. The clinical evidence review did not find evidence that continuous, time-scheduled use of long acting opioids is more effective or safer than intermittent use of short-acting opioids or that time-scheduled use of long acting opioids reduces risks of opioid misuse or addiction (KQ3).

In 2013, the FDA modified the labeling for ER/LA opioid analgesics, 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." 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 short-acting opioids for breakthrough pain when ER/LA opioids are used for chronic pain outside of end-of-life care, and that this practice might be associated with dose escalation.

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 of fatal overdose when methadone or transdermal fentanyl are prescribed to patients who have not used them previously or by providers who are not familiar with their effects.

Experts agreed that providers should not initiate opioid treatment with ER/LA opioids and should not prescribe ER/LA opioids for intermittent use. When opioids are used for chronic pain, as-needed, intermittent dosing with short-acting opioids might minimize total daily opioid dosage compared with continuous use of ER/LA opioids. ER/LA opioids should be reserved for severe, continuous pain. Providers should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or hepatic dysfunction, as decreased clearance of drugs in these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations. While there might be situations in which clinicians need to prescribe short-acting and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to short-acting opioids by temporarily using lower dosages of both), in general, it is preferable to avoid use of short-acting opioids in combination with ER/LA opioids for chronic pain outside of end-of-life care.

When an ER/LA opioid is used, it is preferable to use one with predictable pharmacokinetics and pharmacodynamics 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.

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- 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.
- 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 who are prepared to educate their patients about its use should consider prescribing it.

5. **When opioids are started, providers should prescribe the lowest possible effective dosage. Providers should implement additional precautions when increasing dosage to ≥ 50 MME/day and should avoid increasing dosages to ≥ 90 MME/ day** (strong recommendation, low quality of evidence).

Benefits of high-dose opioids in chronic pain are not established. The clinical evidence review found only one study 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 increased opioid dosages are associated with increased risks of 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 at opioid dosages > 20 MME daily compared with dosages of 1 to 19 MME/day, and that dosages of 50 to 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 to19 MME/day. Dosages ≥ 100 MME/day are associated with increased risks of overdose between 2.0 and 8.9 times the risk at 1 to19 MME/day.

The contextual evidence review found that while there is not a single dosage threshold below which overdose risk is eliminated, holding dosages below 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 of overdose, but that a single dosage threshold for safe opioid use could not be identified. Experts noted that daily opioid dosages less than 50 MME/day are safer than dosages between 50 and 100 MME/day, and that dosages less than 20 MME/day are safer than dosages between 20 and 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 agreed that additional precautions should be taken when patients are prescribed daily opioid dosages of ≥ 50 MME/day and that opioid dosages should generally not be increased to ≥ 90 MME/day.

When opioids are used for chronic pain outside of 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 ≥ 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, because overdose risk increases with increases in opioid dosage. 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 patient's household members (see Recommendation 8). Providers should 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 and should consider working with patients to taper and discontinue opioids (see Recommendation 7).

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

   The clinical evidence review found that opioid use for acute pain is associated with long-term opioid use and that a greater amount of early opioid exposure is associated with greater risk of long-term use (KQ5). Several guidelines on opioid prescribing for acute pain have recommended prescribing ≤ 3 days of opioids in most cases (152-156). Given 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 should also 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. In most cases of acute pain not related to major surgery or trauma, three or fewer days' supply of opioids will be sufficient. Providers should consider a default of three or fewer days of opioids for acute pain, and adjust the duration based on the circumstances of the pain syndrome or surgical procedure. Providers should not prescribe additional opioids to patients "just in case" pain continues longer than expected. Providers should re-evaluate patients who experience 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 such as respiratory depression with ER/LA opioids, providers should not prescribe ER/LA opioids for the treatment of acute pain.

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

   While the clinical evidence review did not find studies evaluating the effectiveness of more frequent monitoring intervals (KQ4), it found that continuing opioid therapy for 3 months substantially increases risk of opioid use disorder (KQ2). In addition, risk of 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. While evidence is insufficient to determine at what point within the first 3 months of opioid therapy the risks for opioid use disorder increase, re-assessment 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 of opioid overdose are greatest during the first 3 to 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

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MME/day or greater. 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, and quality of life, using tools such as the three-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale (149) 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 effects that might be early warning signs for more serious problems such as overdose or opioid use disorder (e.g., sedation, wanting to take opioids in greater quantities or more frequently than prescribed). Because of potential changes in the balance of benefits and risks of opioid therapy over time, providers should regularly reassess at least every 3 months whether opioids continue to meet treatment goals including sustained improvement in pain and function, whether the patient has experienced common or serious adverse effects, whether benefits of opioids continue to outweigh risks, and whether opioid dosage can be reduced or opioids can be discontinued. 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 request dosage reduction or discontinuation, or if patients experience overdose or other serious adverse events (e.g., an event leading to hospitalization or disability), providers should work with patients to reduce opioid dosage and to discontinue opioids when possible.

Considerations for tapering opioids

While 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 dosage weekly by 10%-50% of the original dosage have been recommended by other clinical guidelines (157), and a rapid taper over 2-3 weeks has been recommended in the case of a severe adverse event such as overdose (23). 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, 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 need to be paused and restarted again when the patient is ready and might need 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., patients who have experienced overdose on their current dosage). Ultra-rapid detoxification under anesthesia is associated with substantial risks including death and should not be used (158). Providers should access appropriate expertise if considering tapering opioids during pregnancy. 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 of overdose on abrupt return to a previously prescribed higher dose. Non-opioid pain management (see Recommendation 1) as well as psychosocial support for anxiety related to the taper should be optimized. The Washington State Agency Medical Directors' Group (2015) Interagency Guideline on Prescribing Opioids for Pain, Appendix on Reducing or Discontinuing Chronic Opioid Analgesic Therapy, available at http://www.agencymeddirectors.wa.gov/guidelines.asp (23), and the review "Tapering long-term opioid therapy in chronic non-cancer pain: evidence and recommendations for everyday practice,"(159) available at http://www.mayoclinicproceedings.org/article/S0025-6196(15)00303-1/pdf, contain more detailed guidance on tapering, including management of withdrawal symptoms. 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-related harms are present** (strong recommendation, very low quality of evidence).

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.

Patients with sleep-disordered breathing
Risk factors for sleep-disordered breathing include sleep apnea, congestive heart failure, and obesity. Experts noted that careful monitoring and cautious dose titration should be used if opioids are used in 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).

Pregnant women
Providers should avoid initiating opioid therapy in pregnant women whenever possible given that opioid therapy during pregnancy has been associated with stillbirth, poor fetal growth, pre-term delivery, neonatal abstinence syndrome, and birth defects (contextual evidence review). For pregnant women already on 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).

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 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 may have increased susceptibility to accumulation of opioids and reduced 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 may 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 ≥ 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 over time. Providers should also implement interventions to mitigate common risks of opioid therapy in older adults, such as exercise and/or bowel regimens to mitigate constipation, risk assessment for falls, and patient monitoring for cognitive impairment.

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Patients with mental health conditions

Experts noted that providers should use additional caution and increased monitoring (see Recommendation 7) to mitigate potentially increased risk of opioid use disorder among patients with mental health conditions (including depression, anxiety disorders, and post-traumatic stress disorder (PTSD)), as well as increased risk of drug overdose among patients with depression. 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 of 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 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 drug and alcohol use and 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/or overdose. Providers should also provide specific counseling on increased risks of 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), though 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 end-of-life care in 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 below) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed. Experts also noted the importance of communicating with patients' substance use disorder treatment providers if 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 in 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). Experts agreed that it is preferable not to initiate opioid treatment that places patients at increased risk for opioid-related harms. There were divergent opinions regarding how likely naloxone is to be 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 of overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients taking benzodiazepines with opioids, patients at risk 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). In addition, experts thought providers could consider offering naloxone when prescribing opioids to patients who live with persons with opioid use disorder. 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.

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

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 each opioid prescription written (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 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 (20), 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 is available to prescribers in the PDMP. 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, which might adversely affect patient safety.

The contextual review found there is 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 some states where ability to delegate access to other members of the health care team is permitted, 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 opioid therapy and periodically during long-term opioid therapy. There was disagreement 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 have received from additional prescribers to determine whether a patient is receiving excessive total opioid dosages or dangerous combinations (e.g., opioids combined with benzodiazepines) that put him/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). Such a practice 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 the value of PDMP data in identifying patient risks.

If patients are found to have multiple controlled substance prescriptions written by different providers, there are several actions that can 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 may be incorrect (e.g., if another person has used the patient's identity to obtain prescriptions). Providers should discuss safety concerns with patients found to be receiving medications that put them at increased risk for respiratory depression and overdose when combined with opioids (e.g., benzodiazepines).
- If patients are receiving benzodiazepines, providers should avoid whenever possible prescribing opioids if not yet started, and consider tapering opioids if already initiated (see Recommendations 11 and 7).
- 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 their 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 patients and inform them 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 life-saving information (e.g., risks of opioids, overdose prevention) and interventions (e.g., safer prescriptions, non-opioid pain treatment (see Recommendation 1), naloxone (see Recommendation 8), effective treatment for substance use disorder (see Recommendation 12)).

10. **Providers should use urine drug testing before starting opioids for chronic pain and consider urine drug testing at least annually for all patients on long-term opioid therapy to assess for prescribed medications as well as other controlled substances and illicit drugs** (weak recommendation, very low quality of evidence).

Concurrent use of opioid pain medications with other opioid pain medications, benzodiazepines, or heroin can increase patients' risk of 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 patients who 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 sometimes 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 might de-stigmatize their use. Experts noted that in addition to direct costs of urine drug testing, provider time is needed to interpret, confirm, and communicate results.

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 non-prescribed 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.

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. The Washington State Agency Medical Directors' Group (2015) Interagency Guideline on Prescribing Opioids for Pain, Appendix on Urine Drug Testing, available at http://www.agencymeddirectors.wa.gov/guidelines.asp (23) contains detailed guidance on interpretation of urine drug test results, including tests to order and expected results, drug detection time in urine, drug metabolism, and other considerations. 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 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. 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/discontinuation of opioids (see Recommendation 7), more frequent re-evaluation (see Recommendation 7), offering naloxone (see Recommendation 8), and/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, as this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including obtaining opioids from alternative sources and missed opportunities to facilitate treatment for substance use disorder.

11. **Providers should avoid prescribing of opioid pain medication and benzodiazepines concurrently whenever possible** (strong recommendation, low quality of evidence).

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 of concurrent benzodiazepine use in large proportions of opioid-related overdose deaths in epidemiologic series, 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 (160). Experts agreed that providers should avoid prescribing opioids concurrently with benzodiazepines whenever possible. Providers should taper benzodiazepines gradually if discontinued because abrupt withdrawal can be associated with hallucinations, seizures, and in rare cases, death (contextual evidence review). A commonly used tapering schedule that has been used safely and with moderate success in both elderly and younger patients is a reduction of the benzodiazepine dose by 25% every one to two weeks (161, 162). CBT increases tapering success rates and might be particularly helpful for patients struggling with a benzodiazepine taper (161). Because of greater risks of benzodiazepine withdrawal relative to opioid withdrawal, when patients require tapering of benzodiazepines and/or opioids to reduce risk of fatal respiratory depression, it might be safer and more practical to taper opioids first (see Recommendation 7). Experts emphasized that providers should communicate with mental health professionals managing the patient in order to coordinate care. In addition, if benzodiazepines prescribed for anxiety are tapered or discontinued, evidence-based psychotherapies (e.g., CBT) and/or specific anti-depressants or other non-benzodiazepine medications approved for anxiety should be offered to patients.

12. **Providers should offer or arrange evidence-based treatment (usually opioid agonist treatment in combination with behavioral therapies) for patients with opioid use disorder** (strong recommendation, low quality of evidence).

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) (163).

The clinical evidence review found prevalence of opioid dependence in primary care settings among patients with chronic pain on opioid therapy to be between 3% and 26% (KQ2). Opioid agonist treatment with buprenorphine or methadone maintenance therapy in combination with behavioral therapies has been demonstrated to be more effective in preventing relapse among patients with opioid use disorder than detoxification without maintenance medication (164, 165). However, treatment need in a community is often not met by capacity to provide buprenorphine or methadone maintenance therapy (166). Oral or long-acting injectable formulations of naltrexone may also be used as medication-assisted treatment for opioid use disorder in non-pregnant adults, particularly for highly motivated persons (167, 168). 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 on 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 *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) criteria (see http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf) (163). 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 opioid agonist treatment with buprenorphine or methadone maintenance therapy in combination with behavioral therapies) for opioid use disorder. 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 re-assess for opioid use disorder and offer opioid agonist therapy if criteria are met.

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Physicians not already certified to provide buprenorphine in an office-based setting can undergo training to receive a waiver 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 a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) to prescribe buprenorphine for opioid use disorder. Information about qualifications and the process to obtain a waiver are available from SAMHSA (169). The American Society of Addiction Medicine National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use (170), available at http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/national-practice-guideline.pdf?sfvrsn=22, contains additional guidance on induction, use, and monitoring of buprenorphine treatment for opioid use disorder (see Part 5).

Providers unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a substance use disorder treatment specialist who can provide medication-assisted therapy such as an office-based buprenorphine treatment provider or an opioid treatment program. Providers should assist patients in finding qualified treatment providers and should arrange for patients to follow up with these providers and/or for ongoing coordination of care. Providers should not dismiss patients from their practice because of a substance use disorder as this can adversely affect patient safety and could represent patient abandonment. Identification of substance use disorder represents an opportunity for a provider to provide potentially life-saving interventions, and it is important for the provider to collaborate with the patient regarding their safety in order to increase the likelihood of successful treatment.

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 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.

Future Directions

Clinical guidelines represent one strategy to improve 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 is dedicated to translating 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 engaging 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, 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. Clinical guidelines complement other strategies aimed at preventing illnesses and injuries that lead to pain, 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 (171).

This guideline provides recommendations that are based on the best available evidence 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 in the National Pain Strategy (171) and also 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" (172). The NIH panel recommended that research is

needed to understand 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). 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.

Financial Support

CDC provided 100% of the funding for the supplemental evidence review tasks and meeting support. No foundation or industry support was accepted.

Acknowledgements

Members of the Core Expert Group including Pam Archer, Jane Ballantyne, Amy Bohnert, Bonnie Burman, Roger Chou, Phillip Coffin, Gary Franklin, Erin Krebs, Mitchel Mutter, Lewis Nelson, Trupti Patel, Christina A. Porucznik, Robert "Chuck" Rich, Joanna Starrels, Michael Steinman, Thomas Tape, and Judith Turner; the Core Expert Group facilitator Don Teater; members of the Stakeholder Review Group including John Markman (American Academy of Neurology), Bob Twillman (American Academy of Pain Management), Edward C. Covington (American Academy of Pain Medicine), Roger F. Suchyta (American Academy of Pediatrics), Christina Hielsberg (American Academy of Physical Medicine and Rehabilitation), Richard Wender and Mark Fleury (American Cancer Society), Penney Cowan (American Chronic Pain Association), David Juurlink (American College of Medical Toxicology), Gerald "Jerry" F. Joseph (American College of Obstetrics and Gynecology), Mary Jordan Samuel (American Geriatrics Society), Ashley Thompson (American Hospital Association), Barry Dickinson, Steve Stack, and Patrice Harris (American Medical Association), Gregory Terman (American Pain Society), Beth Haynes (American Society of Addiction Medicine), Asokumar Buvanendran (American Society of Anesthesiologists), Robert M. Plovnick (American Society of Hematology), Sanford M. Silverman (American Society of Interventional Pain Physicians), and Andrew Kolodny (Physicians for Responsible Opioid Prescribing); peer reviewers including Jeanmarie Perrone (University of Pennsylvania), Matthew Bair (Indiana University School of Medicine), and David Tauben (University of Washington); Federal partners including Richard Kronick and Deborah G. Perfetto (AHRQ), Jeffrey A. Kelman and Diane L. McNally (CMS), Jonathan Woodson, Dave Smith, Jack Smith, and Christopher Spevak (DoD), Stephen M. Ostroff and Christopher M. Jones (FDA), Jim Macrae and Alexander F. Ross (HRSA), Nora Volkow and David Thomas (NIDA), John Howard and Douglas Trout (NIOSH), Karen B. DeSalvo and Jennifer Frazier (ONC), Michael Botticelli and Cecelia McNamara Spitznas (ONDCP), Kana Enomoto and Jinhee Lee (SAMHSA), and Robert McDonald and Jack M. Rosenberg (VA); members of the public who provided comment during the webinar; Abt Associates including Douglas McDonald, Brandy Wyant, Kenneth Carlson, and Amy Berninger; and CDC colleagues including Thomas Frieden, Illeana Arias, Debra Houry, Grant Baldwin, Rita Noonan, Julie Gilchrist, Terry Davis, Wes Sargent, Brian Manns, Lisa Garbarino, Donavan Newton, Joann Kang, Noah Aleshire, Jennifer VanderVeur, LeShaundra Scott, Sarah Lewis, Helen Kingery, Kristen Sanderson, Kate Fox, Leslie Dorigo, and Leonard J. Paulozzi.

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SUMMARY RECOMMENDATIONS

Determining When to Initiate or Continue Opioids for Chronic Pain Outside of End-of-Life Care

1. Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Providers should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks (strong recommendation, low quality of evidence).

2. Before starting long-term opioid therapy, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (strong recommendation, very low quality of evidence).

3. Before starting and periodically during opioid therapy, providers should discuss with patients risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy (strong recommendation, low quality of evidence).

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

4. When starting opioid therapy, providers should prescribe short-acting opioids instead of extended-release/long-acting (ER/LA) opioids (strong recommendation, very low quality of evidence).

5. When opioids are started, providers should prescribe the lowest possible effective dosage. Providers should implement additional precautions when increasing dosage to $\geq$ 50 MME/day and should avoid increasing dosages to $\geq$ 90 MME/day (strong recommendation, low quality of evidence).

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

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

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 strategies into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid-related harms are present (strong recommendation, very low quality of evidence).

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

10. Providers should use urine drug testing before starting opioids for chronic pain and consider urine drug testing at least annually for all patients on long-term opioid therapy to assess for prescribed medications as well as other controlled substances and illicit drugs (weak recommendation, very low quality of evidence).

11. Providers should avoid prescribing of opioid pain medication and benzodiazepines concurrently whenever possible (strong recommendation, low quality of evidence).

12. Providers should offer or arrange evidence-based treatment (usually opioid agonist treatment in combination with behavioral therapies) for patients with opioid use disorder (strong recommendation, low quality of evidence).

TABLE 1. GRADE Clinical Evidence Review Ratings

Outcome	Studies	Limitations	Inconsistency	Imprecision	Strength 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	–	–	–	Very low	–	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	Low	–	One retrospective cohort study found prescribed 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	Very low	–	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	Low	–	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	Low	–	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	Low	–	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	Low	–	Long-term opioid use associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI = 1.1 - 1.9).

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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	Low	–	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 percent CI = 10 to 21) for 1 to 36 MME/day, 29 (95 % CI = 20 to 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	Low	Magnitude of effect, dose response relationship	Versus 1 to 19 MME/day, 1 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; 1 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	Low	–	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	Low	–	Relative to a cumulative dose of 0 to 1350 MME over 90 days, the incidence rate ratio for myocardial infarction for 1350 to <2700 MME was 1.21 (95% CI = 1.02 - 1.45), for 2700 to <8100 MME was 1.42 (95% CI = 1.21 - 1.67), for 8100 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	Low	–	No association between opioid dose and risk of motor vehicle crash injuries.

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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	Low	–	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 short-acting 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	Very low	–	Trials on effects of titration with short-acting 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	Very low	–	One new cross-sectional study found initiation of therapy with an ER/LA opioid associated with increased risk of overdose versus initiation with a short-acting opioid (adjusted HR 2.33, 95% CI = 1.26 - 4.32).

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Comparative effectiveness of different ER/LA opioids							
Pain and function	3 randomized trials (*n* = 1,850)	Serious limitations	No inconsistency	No imprecision	Low	–	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	Very low	–	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 in 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	Very low	–	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 short-acting opioids							
Endocrinologic harms	New for update: 1 cross-sectional study (*n* = 1,585)	Serious limitations	Unknown (1 study)	No imprecision	Very low	–	One cross-sectional study found ER/LA opioids associated with increased risk of androgen deficiency versus short-acting opioids (adjusted OR 3.39, 95% CI = 2.39 - 4.77).

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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	Low	–	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).
Short-acting versus ER/LA opioids; short-acting 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	–	–	–	Very low	–	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	Very low	–	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	Very low	–	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3 - 6 months
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Risk assessment and risk mitigation strategies (KQ4)

Diagnostic accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse in 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	Very low	–	Based on a cutoff 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	Low	–	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity of 0.38 in 1 study, for a positive likelihood ratio of 1.11 and a negative likelihood ratio of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in 1 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	Low	–	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 2 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	Low	–	Based on a "high risk" assessment, sensitivity was 0.73 and 0.83 and specificity was 0.43 and 0.88 in 2 studies, for positive likelihood ratios of 1.28 and 7.18 and negative likelihood ratios of 0.63 and 0.19.
Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain							
Outcomes related to abuse	None	–	–	–	Very low	–	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	–	–	–	Very low	–	No evidence
Comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids							
Outcomes related to abuse	None	–	–	–	Very low	–	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	Low	–	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 1-140 MME/day and OR 6.14, 95% CI = 4.92 - 7.66 for ≥450 MME/day).

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

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Appendix A

Steering Committee and Core Expert Group Members

Steering Committee

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Appendix B

Core Expert Group (CEG) Disclosures

The Core Expert Group (CEG) members wish to disclose 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 there is no bias. CEG members wish to disclose the following activities related to the content of this guideline: Jayne Ballantyne wishes to disclose 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 (REMS) committee; Phillip Coffin wishes to disclose that in 2012 he provided expert testimony to the California State Assembly regarding a bill to expand naloxone access and wishes to report that he is the principal investigator on a research study of methamphetamine dependence that receives donated Vivitrol (injectable naltrexone) from Alkermes Inc.; Erin Krebs wishes to disclose that she represented the American College of Physicians at a 2014 Food and Drug Administration meeting on Abuse Deterrent Opioid Formulations; Lewis Nelson wishes to disclose his ad-hoc membership on the FDA Drug Safety and Risk Management Advisory Committee; Robert "Chuck" Rich wishes to disclose that he was an author on the 2013 American Academy of Family Physicians position paper on opioids and pain management; Joanna Starrels wishes to disclose that she received honoraria from the Betty Ford Institute; Thomas Tape wishes to disclose that he was an author on the 2013 American College of Physicians policy position paper on prescription drug abuse.

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Appendix C

Stakeholder Review Group

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