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

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Abstract

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

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

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

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

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

CONCLUSIONS AND RELEVANCE—The guideline is intended to improve communication about benefits and risks of opioids for chronic pain, improve safety and effectiveness of pain treatment, and reduce risks associated with long-term opioid therapy.

The number of people experiencing chronic pain is substantial, with US prevalence estimated at 11.2% of the adult population.[1] Patients should receive appropriate pain treatment based on a careful consideration of the benefits and risks of treatment options. Opioids are commonly prescribed for pain, with approximately 3% to 4% of the adult US population prescribed long-term opioid therapy.[2] Evidence supports short-term efficacy of opioids in randomized clinical trials lasting primarily 12 weeks or less,[3] and patients

receiving opioid therapy for chronic pain report some pain relief when surveyed.[4–6] However, few studies have been conducted to rigorously assess the long-term benefits of opioids for chronic pain (pain lasting >3 months) with outcomes examined at least 1 year later.[7] Opioid pain medication use presents serious risks. From 1999 to 2014, more than 165 000 persons died of overdose related to opioid pain medication in the United States.[8] In 2013 alone, an estimated 1.9 million persons abused or were dependent on prescription opioid pain medication.[9] Primary care clinicians report concern about opioid pain medication misuse, find managing patients with chronic pain stressful, express concern about patient addiction, and report insufficient training in prescribing opioids.[10]

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

The guideline is intended to improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death. Clinical decision making should be based on a relationship between the clinician and patient and an understanding of the patient’s clinical situation, functioning, and life context. The recommendations in the guideline are voluntary, rather than prescriptive standards. They are based on emerging evidence, including observational studies or randomized clinical trials with notable limitations. Clinicians should consider the circumstances and unique needs of each patient when providing care. This Special Communication details evidence reviewed by and official recommendations issued by the Centers for Disease Control and Prevention (CDC) and provides key highlights from a more extensive guideline; the full guideline with detailed information on disclosures and conflict of interest protocols, methods, scientific findings, and recommendation rationales can be found in the *Morbidity and Mortality Weekly Report* (*MMWR*).[11]

Guideline Development Process

Grading of Recommendations Assessment, Development, and Evaluation Method

CDC used the CDC Advisory Committee on Immunization Practices (ACIP) translation[12] of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method for guideline development.[13] Within the ACIP GRADE framework, the quality of a body of evidence was graded, and the recommendations were developed and placed into categories (A or B) based on the quality of evidence, balance of benefits and harms, values and preferences, and resource allocation (Box 1).

CDC obtained input from experts, stakeholders, the public, peer reviewers, and a federally chartered advisory committee in the development process. CDC drafted a set of recommendations and invited subject matter experts, primary care professional society representatives, and state agency representatives (Core Expert Group, listed at the end of the article) to provide individual perspectives on how CDC used the evidence to develop the recommendations. CDC asked experts to undergo a rigorous process to assess and manage possible conflicts of interest; full details on protocols and disclosures are reported in the *MMWR*.[11] CDC also engaged partners from 10 federal agencies and a Stakeholder Review Group of 18 organizations (listed at the end of the article) to provide comment. CDC convened a constituent engagement webinar to obtain additional perspectives from constituents on the key recommendations. To obtain comments from the public on the full guideline, CDC published a notice in the *Federal Register* (80 FR 77351) announcing the avail-ability of the guideline and the supporting clinical and contextual evidence reviews for public comment. Per the final information quality bulletin for peer review (https://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2005/m05–03.pdf), the guideline was peer reviewed because it provides influential scientific information. In addition, the National Center for Injury Prevention and Control Board of Scientific Counselors (BSC), a federal advisory committee, established an Opioid Guideline Workgroup (OGW) to review the guideline (members of the BSC and OGW are listed at the end of the article). The OGW issued a report of observations to the BSC. At an in-person meeting, the BSC considered the OGW report, deliberated on the draft guideline itself, and offered an additional opportunity for public comment. The BSC voted unanimously to support the observations made by the OGW; that CDC adopt the guideline recommendations that, according to the workgroup's report, had unanimous or majority support; and that CDC further consider the guideline recommendations for which the group had mixed opinions. At each stage, CDC reviewed and carefully considered comments and revised the guideline.

Clinical Evidence Review

To inform the guideline development process, CDC updated a systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ) on the effectiveness and risks of long-term opioid treatment of chronic pain[7] that addressed clinical questions about effectiveness of long-term opioid therapy for outcomes at least 1 year later related to pain, function, and quality of life. The effectiveness of short-term opioid therapy has been established previously. In randomized clinical trials 12 weeks or shorter in duration, opioids were moderately effective for pain relief, with small benefits for functional outcomes; although estimates varied, based on uncontrolled studies, a high percentage of patients discontinued long-term opioid use because of lack of efficacy and because of adverse events.[3] Opioids have unique effects such as tolerance and physical dependence that might influence assessments of benefit over time. These effects raise questions about whether findings on short-term effectiveness of opioid therapy can be extrapolated to estimate benefits of long-term therapy for chronic pain. Thus, it is important to consider studies that provide data on long-term benefit. For opioid-related harms (overdose, fractures, falls, motor vehicle crashes), studies were included with outcomes measured at shorter intervals because such outcomes can occur early during opioid therapy.

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

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

The updated review revealed that evidence on long-term opioid therapy for chronic pain outside of end-of-life care remains limited, with insufficient evidence to determine long-term benefits, although evidence suggests risk of serious harms that is dose-dependent. Table 1 provides a summary of the evidence and the quality ratings assigned. Full details on methodology and findings are available in the 2014 AHRQ report[7] and the *MMWR* report.[11] The body of evidence for each clinical question was categorized as evidence type 3 or 4 (observational studies or randomized clinical trials with notable limitations or clinical experience and observation).We highlight important findings from the review for each key question (KQ) below.

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

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

Long-term opioid therapy was associated with an increased risk of an opioid abuse or dependence diagnosis (as defined by *ICD-9-CM* codes) vs no opioid prescription.[14] In primary care settings, prevalence of opioid dependence (using *DSM-IV* criteria) ranged from 3% to 26%.[15–17] Factors associated with increased risk of misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications.

[16,18] Opioid use was associated with a dose-dependent increased risk of fatal and non-fatal overdose[19,20] (Table 2). Other risks associated with opioid use included cardiovascular events,[28,29] endocrinologic harms,[30,31] and road trauma.[32]

KQ3: Dosing Strategies—Initiation of therapy with an extended-release/long-acting(ER/LA) opioid was associated with greater risk of nonfatal overdose than initiation with an immediate-release opioid in 1 study, with risk greatest in the first 2 weeks after initiation of treatment.[33] Three studies of various ER/LA opioids found no clear differences related to pain or function[34–36]; there were mixed findings regarding the differences between methadone and morphine in overall risk for nonfatal or fatal overdose,[37–39] suggesting that risks of methadone might vary in different settings. One study found no differences between more liberal dose escalation and maintenance of current doses after 12 months[40]; evidence on other comparisons related to opioid dosing strategies was too limited to determine effects on outcomes.

KQ4: Risk Assessment and Risk Mitigation Strategies—Evidence on the accuracy of risk assessment instruments for predicting opioid abuse or misuse was inconsistent for the Opioid Risk Tool[41–43] and limited for other risk assessment instruments.[41,44,45] No study evaluated the effectiveness of risk mitigation strategies.

KQ5: Effect of Opioid Therapy for Acute Pain on Long-term Use—Studies examining patients who underwent low-risk surgery or experienced low back pain from injury revealed that opioid therapy prescribed for acute pain was associated with greater likelihood of long-term use.[46,47] Compared with no early opioid use for acute low back pain, the adjusted odds ratio for receiving 5 or more opioid prescriptions from 30 to 730 days after onset was 2.08 (95% CI, 1.55–2.78) for 1 to 140 morphine milligram equivalents (MME) per day and increased to 6.14 (95% CI, 4.92–7.66) for 450 MME or more per day.[47]

Contextual Evidence Review

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

Several nonpharmacologic and nonopioid pharmacologic treatments were found to be effective for chronic pain in studies ranging in duration from 2 weeks to 6 months[48–66] (Table 3). For example, cognitive behavioral therapy (CBT) had small positive effects on disability and catastrophic thinking.[66] Exercise therapy reduced pain and improved function

in chronic low back pain[54]; improved function and reduced pain in osteoarthritis of the knee[51] and hip[52]; and improved well-being, fibromyalgia symptoms, and physical function in fibromyalgia.[48] Multimodal and multidisciplinary therapies helped reduce pain and improve function more effectively than single modalities.[55,67] Multiple guidelines recommended acetaminophen as first-line pharmacotherapy for osteoarthritis[68–73] or for low back pain[74] and nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line treatment for osteoarthritis or low back pain[70,74]; first- and second-line drugs for neuropathic pain include anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors (SNRIs).[75–78] Nonsteroidal anti-inflammatory drugs have been associated with hepatic, gastrointestinal, renal, and cardiovascular risks.[63,73,79]

Opioid-related overdose risk was dose-dependent, with higher opioid dosages associated with increased overdose risk (Table2).[19–27] Compared with dosages of 1 to <20 MME per day, dosages of 50 to <100 MME per day were found to increase risks for opioid overdose by factors of 1.9[20] to 4.6,[22] with absolute risk difference approximation of 0.15% for fatal overdose[22] and 1.40% for any overdose;[19] dosages of 100 MME or more per day were found to increase risks for opioid overdose by factors of 2.0[20] to 8.9[19] relative to dosages of 1 to <20 MME per day, with absolute risk difference approximation 0.25% for fatal overdose[22] and 4.04% for any overdose.[19] Veterans Health Administration patients with chronic pain who died of overdoses related to opioids were prescribed higher mean opioid dosages (98 MME/d) than controls (48 MME/d)[27]; above 200 MME per day, mortality rates continue to increase more gradually.[23] (See Table 4 and Box 4 for a list of common opioid medications and their MME equivalents.)

Other findings included disproportionate numbers of overdose deaths associated with methadone[80]; fatal overdose risk associated with co-prescription of opioids and benzodiazepines[20,23,81]; and risks associated with sleep-disordered breathing,[82,83] reduced renal or hepatic function,[84] older age,[85–88] pregnancy,[89–92] mental health comorbidities, and history of substance use disorder.[18,93,94] Indirect evidence was found for potential utility of risk stratification and mitigation strategies for identifying risky opioid-taking behaviors and prescribing practices, such as checking prescription drug monitoring program (PDMP) data[95] and urine drug testing,[96] as well as co-prescription of naloxone.[97] In addition, methadone and buprenorphine for opioid use disorder were found to increase retention in treatment and to decrease illicit opioid use among patients with opioid use disorder, and some studies suggest that effectiveness is enhanced when psychosocial treatments are used in conjunction with medication-assisted therapy.[98–102]

Recommendations

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

- No evidence shows a long-term benefit of opioids in pain and function vs no opioids for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized clinical trials ≤6 weeks in duration).

- Extensive evidence shows the possible harms of opioids (including opioid use disorder, overdose, and motor vehicle injury).
- Extensive evidence suggests some benefits of nonpharmacologic and nonopioid pharmacologic therapy, with less harm.

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate. (Recommendation category: A; evidence type: 3)

Nonpharmacologic therapy (such as exercise therapy and CBT) should be used to reduce pain and improve function in patients with chronic pain. Aspects of these approaches can be used even when there is limited access to specialty care. For example, primary care clinicians can encourage patients to take an active role in the care plan and support patients in engaging in exercise. Nonopioid pharmacologic therapy (such as NSAIDs, acetaminophen, anticonvulsants, and SNRIs) should be used when benefits outweigh risks and should be combined with nonpharmacologic therapy. Opioids should not be considered first-line or routine therapy for chronic pain outside of active cancer, palliative, and end-of-life care, given small to moderate short-term benefits, uncertain long-term benefits, and potential for serious harms; although evidence on long-term benefits of nonopioid therapies is also limited, these therapies are also associated with short-term benefits, and risks are much lower. This does not mean that patients should be required to sequentially “fail” nonpharmacologic and nonopioid pharmacologic therapy before proceeding to opioid therapy. Rather, expected benefits specific to the clinical context should be weighed against risks before initiating therapy. In some clinical contexts (eg, headache, fibromyalgia), expected benefits of initiating opioids are unlikely to outweigh risks regardless of previous nonpharmacologic and nonopioid pharmacologic therapies used. In other situations (eg, serious illness in a patient with poor prognosis for return to previous level of function, contraindications to other therapies, and clinician and patient agreement that the overriding goal is patient comfort), opioids might be appropriate regardless of previous therapies used. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate, to provide greater benefits to patients.

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

Before opioid therapy is initiated for chronic pain, clinicians should determine how effectiveness will be evaluated and should establish treatment goals with patients. Clinicians seeing new patients already receiving opioids should establish treatment goals for continued

treatment. Goals should include improvement in both pain relief and function. However, there are some clinical circumstances under which reductions in pain without improvement in physical function might be a more realistic goal (eg, diseases typically associated with progressive functional impairment or catastrophic injuries such as spinal cord trauma). Experts noted that function can include emotional and social as well as physical dimensions. In addition, experts emphasized that mood has important interactions with pain and function. Clinicians may use validated instruments such as the 3-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale[103] to track patient outcomes. Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function.[104] Because depression, anxiety, and other psychological comorbidities often coexist with and can interfere with resolution of pain, clinicians should use validated instruments to assess for these conditions and ensure that treatment for these conditions is optimized.

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

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

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

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

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

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

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

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

- Methadone should not be the first choice for an ER/LA opioid. Only clinicians who are familiar with methadone's unique risk profile and who are prepared to educate and closely monitor their patients—including risk assessment for QT prolongation and consideration of electrocardiographic monitoring—should consider prescribing methadone for pain.
- Because dosing effects of transdermal fentanyl are often misunderstood by both clinicians and patients, only clinicians who are familiar with the dosing and absorption properties of transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.

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

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

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

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

Acute pain can often be managed without opioids. When diagnosis and severity of nontraumatic, nonsurgical pain are reasonably assumed to warrant the use of opioids, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids, often 3 days or less, unless circumstances clearly warrant additional opioid therapy. More than 7 days will rarely be needed. Postsurgical pain is outside the scope of this guideline but has been addressed elsewhere.[106] Clinicians should not prescribe additional opioids to patients "just in case" pain continues longer than expected. Clinicians should reevaluate the subset of patients who experience severe acute pain that continues longer than the expected duration to confirm or revise the initial

diagnosis and to adjust management accordingly. Clinicians should not prescribe ER/LA opioids for the treatment of acute pain.

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

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

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

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

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

needed to optimize nonopioid pain management, as well as psychosocial support for anxiety related to the taper.

Assessing Risk and Addressing Harms of Opioid Use

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

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

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

9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months. (Recommendation category: A; evidence type: 4)

Clinicians should review PDMP data for opioids and other controlled medications patients might have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or dangerous combinations (eg, opioids combined with

benzodiazepines) that put him or her at high risk for overdose. Ideally, PDMP data should be reviewed before every opioid prescription. This is recommended in all states with well-functioning PDMPs and where PDMP access policies make this practicable (eg, clinician and delegate access permitted), but it is not currently possible in states without functional PDMPs or in those that do not permit certain prescribers to access them.

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

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

Clinicians should not dismiss patients from their practice on the basis of PDMP information. Doing so could result in missed opportunities to provide potentially lifesaving information and interventions.

10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs. (Recommendation category: B; evidence type: 4)

Prior to starting opioids for chronic pain and periodically during opioid therapy, clinicians should use urine drug testing to assess for prescribed opioids as well as other controlled substances and illicit drugs that increase risk for overdose when combined with opioids, including nonprescribed opioids, benzodiazepines, and heroin.

In most situations, initial urine drug testing can be performed with a relatively inexpensive immunoassay panel for commonly prescribed opioids and illicit drugs. Patients prescribed less commonly used opioids might require specific testing for those agents. The use of confirmatory testing adds substantial costs and should be based on the need to detect specific opioids that cannot be identified on standard immunoassays or on the presence of unexpected urine drug test results. In addition, clinicians should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. Clinicians 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. Before ordering urine drug testing, clinicians should explain to patients that testing is intended to improve their safety, should explain expected results (eg, presence of prescribed medication and absence of drugs, including illicit drugs, not reported by the patient), and should ask patients whether there might be unexpected results. Clinicians should discuss unexpected results with the local laboratory or toxicologist and with the patient. Discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (eg, gas or liquid chromatography/mass spectrometry) might be warranted to clarify the situation.

Clinicians should not dismiss patients from care based on a urine drug test result. This could have adverse consequences for patient safety, including missed opportunities to facilitate treatment for substance use disorder.

11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. (Recommendation category: A; evidence type: 3)

Although there are circumstances when it might be appropriate to prescribe opioids to a patient receiving benzodiazepines (eg, severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible. In addition, given that other central nervous system depressants (eg, muscle relaxants, hypnotics) can potentiate central nervous system depression associated with opioids, clinicians should consider whether benefits outweigh risks of concurrent use of these drugs. Clinicians should check the PDMP for concurrent controlled medications prescribed by other clinicians and should consider involving pharmacists and pain specialists as part of the management team when opioids are co-prescribed with other central nervous system depressants. When patients require tapering of benzodiazepines or opioids to reduce risk of fatal respiratory depression, it might be safer and more practical to taper opioids first. Clinicians should taper benzodiazepines gradually if discontinued because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death. If benzodiazepines

prescribed for anxiety are tapered or discontinued, evidence-based psychotherapies (eg, CBT) and specific antidepressants or other nonbenzodiazepine medications approved for anxiety should be offered. Clinicians should communicate with mental health professionals managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.

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

If clinicians suspect opioid use disorder[107] based on patient concerns or behaviors or on findings in PDMP data or from urine drug testing, they should discuss their concerns with their patient and provide an opportunity for the patient to disclose related concerns or problems. Clinicians should assess for opioid use disorder using *DSM-5* criteria.[108] Clinicians should offer or arrange for patients with opioid use disorder to receive evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone maintenance therapy in combination with behavioral therapies).Oral or long-acting injectable naltrexone can also be used in nonpregnant adults. For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine (without naloxone) or methadone has been associated with improved maternal outcomes and should be offered.

Physicians prescribing opioids in communities without sufficient treatment capacity for opioid use disorder should strongly consider obtaining a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) that allows them to prescribe buprenorphine to treat patients with opioid use disorder.[109] Clinicians do not need a waiver to offer naltrexone for opioid use disorder as part of their practice. Clinicians unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a substance use disorder treatment specialist, such as an office-based clinician who prescribes buprenorphine or naltrexone treatment, or from an opioid treatment program certified by SAMHSA to provide supervised medication-assisted treatment for patients with opioid use disorder.

Discussion

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

Of primary importance, nonopioid therapy is preferred for treatment of chronic pain. Opioids should be used only when benefits for pain and function are expected to outweigh risks. Before starting opioids, clinicians should establish treatment goals with patients and consider how opioids will be discontinued if benefits do not outweigh risks. When opioids

are used, clinicians should prescribe the lowest effective dosage, carefully reassess benefits and risks when considering increasing dosage to 50 MME or more per day, and avoid concurrent opioids and benzodiazepines whenever possible. Clinicians should evaluate benefits and harms of continued opioid therapy with patients every 3 months or more frequently and review prescription drug monitoring program data, when available, for high-risk combinations or dosages. For patients with opioid use disorder, clinicians should offer or arrange evidence-based treatment, such as medication-assisted treatment with buprenorphine or methadone.

Clinical guidelines complement other strategies such as strengthening the evidence base for pain prevention and treatment, reducing disparities in pain treatment, improving service delivery and reimbursement, and supporting professional and public education.[110] To aid the application of the guideline in clinical practice, CDC is translating the guideline into user-friendly materials, such as a checklist decision aid (eFigure in the Supplement), fact sheets (available at http://www.cdc.gov/drugoverdose/prescribing/resources.html),and a mobile application. CDC will also work with partners to support clinician education on pain management options, opioid therapy, and risk mitigation strategies. Efforts that might enhance implementation of recommended practices include development of quality improvement measures, implementing clinical decision support, and integrating initiatives to promote safer prescribing within insurance plans. In addition, policy initiatives that address barriers to implementation of the guideline, such as increasing accessibility of PDMP data, e-prescribing, and availability of clinicians who can offer medication-assisted treatment for opioid use disorder are strategies to consider to enhance implementation of the recommended practices. CDC will work with federal partners and payers to evaluate strategies such as payment reform and health care delivery models that could improve patient health and safety. For example, strategies might include strengthened coverage for non-pharmacologic treatments, appropriate urine drug testing, and medication-assisted treatment; reimbursable time for patient counseling; and payment models that improve access to interdisciplinary, coordinated care.

The CDC guideline provides recommendations that are based on best available evidence, interpreted and informed by expert opinion. Evidence informing the recommendations is based on observational studies or randomized clinical trials with notable limitations, as well as clinical experience and observations, characterized as low in quality under GRADE methodology. As highlighted by a National Institutes of Health expert panel, “evidence is insufficient for every clinical decision that a provider needs to make about the use of opioids for chronic pain.”[111] The expert panel recommended that research is needed to improve current understanding of which types of pain, specific diseases, and patients are most likely to be associated with benefit and harm from opioid pain medications; evaluate andestimatecost-benefitofmultidisciplinarypaininterventions;develop and validate tools for identification of patient risk and outcomes; assess the effectiveness and harms of opioid pain medications with alternative study designs; and investigate risk identification and mitigation strategies and their effects on patient and public health outcomes.

To inform future guideline development, more research is needed to fill critical evidence gaps. Yet given that chronic pain is a significant public health problem, the risks associated

with long-term opioid therapy, the availability of effective alternative treatment options for pain, and the potential for improvement in the quality of health care with the implementation of recommended practices, a guideline for prescribing is warranted with currently available evidence. The balance between benefits and harms of long-term opioid therapy for chronic pain based on both clinical and contextual evidence is sufficiently clear to support the issuance of category A recommendations in most cases.

Conclusions

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1.

Interpretation of Recommendation Categories and Evidence Type

Recommendation Categories

Recommendation categories are based on evidence type, balance between desirable and undesirable effects, values and preferences, and resource allocation (cost).

Category A recommendation:

Applies to all persons; most patients should receive the recommended course of action.

Category B recommendation:

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

Evidence Type

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

Type 1 evidence:

Randomized clinical trials or overwhelming evidence from observational studies.

Type 2 evidence:

Randomized clinical trials with important limitations or exceptionally strong evidence from observational studies.

Type 3 evidence:

Observational studies or randomized clinical trials with notable limitations.

Type 4 evidence:

Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.

Box 2.

Key Questions for the Clinical Evidence Review

Key Question 1. Effectiveness and Comparative Effectiveness

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

Key Question 2. Harms and Adverse Events

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

Key Question 3. Dosing Strategies

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

c. In patients with chronic pain, what is the comparative effectiveness of different ER/LA opioids on outcomes related to pain, function, and quality of life and risk of overdose, addiction, abuse, or misuse?

d. In patients with chronic pain, what is the comparative effectiveness of immediate-release plus ER/LA opioids vs ER/LA opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?

e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous vs as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?

f. In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose escalation vs dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?

g. In patients on long-term opioid therapy, what is the comparative effectiveness of opioid rotation vs maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?

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

i. In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or of tapering off opioids vs continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?

j. In patients on long-term opioid therapy, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?

Key Question 4. Risk Assessment and Risk Mitigation Strategies

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

b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse?

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

d. What is the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and quality of life?

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

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

Key questions 1–4 were developed for the Agency for Healthcare Research and Quality review.[7]

Box 3.

Key Areas for the Contextual Evidence Review

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

Box 4.

Cautions About Calculating Morphine Milligram Equivalent Doses

- Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics.
- Do not use the calculated dose in morphine milligram equivalents (MME) to determine the doses to use when converting one opioid to another; when converting opioids, the new opioid is typically dosed at substantially lower than the calculated MME dose to avoid accidental overdose due to incomplete cross-tolerance and individual variability in opioid pharmacokinetics.
- Use particular caution with methadone dose conversions because the conversion factor increases at higher doses.
- Use particular caution with fentanyl because it is dosed in μg/h instead of mg/d, and its absorption is affected by heat and other factors.

Box 5.

Centers for Disease Control and Prevention Recommendations for Prescribing Opioids for Chronic Pain Outside of Active Cancer, Palliative, and End-of-Life Care

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

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

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to 50 morphine milligram equivalents (MME) or more per day, and should avoid increasing dosage to 90 MME or more per day or carefully justify a decision to titrate dosage to 90 MME or more per day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms

of continued opioid therapy, clinicians should optimize therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

Assessing Risk and Addressing Harms of Opioid Use

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

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

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

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

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

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

Table 1.

GRADE Ratings of the Evidence for the Key Clinical Questions[a]

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of Evidence[b]	Other Factors	Estimates of Effect or Findings
Effectiveness and Comparative Effectiveness (Key Question 1)							
Effectiveness of long-term opioid therapy vs placebo or no opioid therapy for long-term (≥1 y) outcomes							
Pain, function, and quality of life	None	NA	NA	NA	Insufficient	NA	No evidence.
Harms and Adverse Events (Key Question 2)							
Risks of opioids vs placebo or no opioids on opioid abuse, addiction, and related outcomes; overdose; and other harms							
Abuse or addiction	1 cohort study (n = 568 640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found long-term use of prescribed opioids was associated with an increased risk of abuse or dependence diagnosis vs no opioid use (adjusted OR range, 14.9–122.5, depending on dose).
Abuse or addiction	10 uncontrolled studies (n = 3780)	Very serious limitations	Very serious inconsistency	No imprecision	4	None identified	in primary care settings, prevalence of opioid abuse ranged from 0.6%−8%; prevalence of dependence, 3%–26%. In pain clinic settings, prevalence of misuse, 8%−16%, and addiction, 2%–14%. Prevalence of aberrant drug-related behaviors, 6%−37%.
Overdose	1 cohort study (n = 9940)	Serious limitations	Unknown (1 study)	Serious imprecision	3	None identified	Current opioid use associated with increased risk of any overdose events, adjusted HR, 5.2 (95% Cl, 2.1–12), and serious overdose events, adjusted HR, 8.4 (95% Cl, 2.5–28) vs current nonuse.
Fractures	1 cohort study (n = 2341) 1 case-	Serious limitations	No inconsistency	No imprecision	3	None identified	Opioid use associated with increased risk of

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of Evidence[b]	Other Factors	Estimates of Effect or Findings
	controlstudy (n = 21 739 case patients)						fracture in 1 cohort study, adjusted HR, 1.28 (95% Cl, 0.99–1.64), and 1 case-control study, adjusted OR, 1.27 (95% Cl, 1.21–1.33).
Myocardial infarction	1 cohort study (n = 426 124) 1 case-controlstudy (n = 11 693 case patients)	No limitations	No inconsistency	No imprecision	3	None identified	Current opioid use associated with increased risk of myocardial infarction vs nonuse, adjusted OR, 1.28 (95% Cl, 1.19–1.37) and IRR, 2.66 (95% Cl, 2.30–3.08).
Endocrinologic harms	1 cross-sectional study (n = 11327)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement vs nonuse, adjusted OR, 1.5 (95% Cl, 1.1–1.9).
How do harms vary depending on the opioid dose used?							
Abuse or addiction	1 cohort study (n = 568 640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared with no opioid prescription, the adjusted ORs were 15 (95% Cl, 10–21) for 1–36 MM E/d, 29 (95% Cl, 20–41) for 36–120 MM E/d, and 122 (95% Cl, 73–205) for ≥120 MME/d.
Overdose	1 cohort study (n = 9940) and 1 case-control study (n = 593 case patients in primary analysis)	Serious limitations	No inconsistency	No imprecision	3	Magnitude of effect, dose-response relationship	Compared with l-<20 MME/d, 1 cohort study found an adjusted HR for an overdose event of 1,44 (95% Cl, 0.57–3.62) for 20-<50 MME/d that increased to 8.87

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of Evidence[b]	Other Factors	Estimates of Effect or Findings
							(95% Cl, 3.99–19.72) at >100 MME/d; 1 case-control study found an adjusted OR for an opioid-related death of 1,32 (95% Cl, 0.94–1.84) for 20–49 MME/d that increased to 2.88 (95% Cl, 1.79–4.63) at ≥200 MME/d.
Fractures	1 cohort study (n = 2341)	Seriouslimitations	Unknown (1 study)	Serious imprecision	3	None identified	Risk of fracture increased from an adjusted HR of 1.20 (95% Cl, 0.92–1.56) at l-<20 MME/d to 2.00 (95% Cl, 1.24–3.24) at ≥50 MME/d; the trend was of borderline statistical significance.
Myocardial infarction	1 cohort study (n = 426 124)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Relative to a cumulative dose of 0–1350 MME during a 90-d period, the IRR for myocardial infarction for 1350-<2700 MME was 1,21 (95% Cl, 1.02–1.45); for 2700-<8100 MME, 1.42 (95% Cl, 1.21–1.67); for 8100-<18 000 MME, 1.89 (95% Cl, 1,54–2.33); and for >18 000 MME, 1.73 (95% Cl, 1.32–2.26).
Motor vehicle crash injuries	1 case-control study (n = 5300 case patients)	No limitations	Unknown (1 study)	No imprecision	3	None identified	No association between opioid dose and risk of motor vehicle crash injuries even though opioid dosages ≥20 MME/d were associated with increased odds of road trauma among drivers.
Endocrinologic harms	1 cross-sectional study (n = 11327); new for update: 1 additional cross-sectional study (n = 1585)	Serious limitations	Consistent	No imprecision	3	None identified	Relative to 0-<20 MME/d, the adjusted OR for ≥120 MME/d for use of medications for erectile dysfunction or testosterone replacement was 1.6

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of Evidence[b]	Other Factors	Estimates of Effect or Findings
							(95% Cl, 1.0–2.4). One new cross-sectional study found higher-dose long-term opioid therapy associated with increased risk of androgen deficiency among men receiving immediate-release opioids, adjusted OR per 10 MME/d, 1.16 (95% Cl, 1,09–1.23), but the dose response was very weak among men receiving ER/LA opioids.
Dosing Strategies (Key Question 3)							
Comparative effectiveness of different methods for initiating opioid therapy and titrating doses							
Pain	3 randomized trials (n = 93)	Serious limitations	Serious inconsistency	Very serious imprecision	4	None identified	Trials on effects of titration with immediate-release vs ER/LA opioids reported inconsistent results and had additional differences between treatment groups in dosing protocols (titrated vs fixed dosing) and doses of opioids used.
Overdose	New for update: 1 cohort study (n = 840 606)	Serious Limitations	Unknown (1 study)	No imprecision	4	None identified	One new cross-sectional study found initiation of therapy with an ER/LA opioid associated with increased risk of overdose vs initiation with an immediate-release opioid, adjusted HR, 2.33 (95% Cl, 1.26–4.32).
Comparative effectiveness of different ER/LA opioids							

JAMA. Author manuscript; available in PMC 2019 February 26.

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of Evidence[b]	Other Factors	Estimates of Effect or Findings
Pain and function	3 randomized trials (n = 1850)	Serious limitations	No inconsistency	No imprecision	3	None identified	No differences.
All-cause mortality	1 cohort study (n = 108 492); new for update: 1 cohort study (n = 38 756)	Serious limitations	Serious inconsistency	No imprecision	4	None identified	One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity-adjusted analysis, adjusted HR, 0.56 (95% Cl, 0.51–0.62). One cohort study among Tennessee Medicaid patients found methadone to be associated with higher risk of all-cause mortality than sustained-release morphine, adjusted HR, 1.46 (95% Cl, 1.17–1.73).
Abuse and related outcomes	1 cohort study (n = 5684)	Serious limitations	Unknown (1 study)	Serious imprecision	4	None identified	One cohort study found some differences between ER/LA opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions.
ER/LA vs immediate-release opioids							
Endocrinologic harms	New for update: 1 cross-sectional study (n = 1585)	Serious limitations	Unknown (1 study)	No imprecision	4	None identified	One cross-sectional study found ER/LA opioids associated with increased risk of androgen deficiency vs immediate-release opioids, adjusted OR, 3.39 (95% Cl, 2.39–4.77).
Dose escalation vs dose maintenance or use of dose thresholds							

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of Evidence[b]	Other Factors	Estimates of Effect or Findings
Pain, function, or withdrawal due to opioid misuse	1 randomized trial (n = 140)	Serious limitations	Unknown (1 study)	Very serious imprecision	3	None identified	No difference between more liberal dose escalation vs maintenance of current doses in pain, function, or risk of withdrawal due to opioid misuse, but there was limited separation in opioid doses between groups (52 vs 40 MME/d at the end of the trial).
Immediate-release vs ER/LA opioids, immediate-release plus ER/LA opioids vs ER/LA opioids alone, scheduled and continuous vs as-needed dosing of opioids, or opioid rotation vs maintenance of current therapy							
Pain, function, quality of life, and outcomes related to abuse	None	NA	NA	NA	Insufficient	NA	No evidence.
Effects of decreasing or tapering opioid doses vs continuation of opioid therapy							
Pain and function	1 randomized trial (n = 10)	Very serious [imitations	Unknown (1 study)	Very serious imprecision	4	None identified	Abrupt cessation of morphine was associated with increased pain and decreased function compared with continuation of morphine.
Comparative effectiveness of different tapering protocols and strategies							
Opioid abstinence	2 nonrandomized trials (n = 150)	Very serious [imitations	No inconsistency	Very serious imprecision	4	None identified	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3–6 mo.

JAMA. Author manuscript; available in PMC 2019 February 26.

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of Evidence[b]	Other Factors	Estimates of Effect or Findings
Risk Assessment and Risk Mitigation Strategies (Key Question 4)							
Diagnostic accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse among patients with chronic pain being considered for long-term opioid therapy							
Opioid Risk Tool	3 studies of diagnostic accuracy (n = 496); new for update: 2 studies of diagnostic accuracy (n = 320)	Serious limitations	Very serious inconsistency	Serious imprecision	4	None identified	Based on a cutoff score of >4 (or unspecified), 5 studies (2 fair-quality, 3 poor-quality) reported sensitivity that ranged from 0.20–0.99 and specificity that ranged from 0.16–0.88.
Screener and opioid assessment for patients with pain, version 1	2 studies of diagnostic accuracy (n = 203)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity was 0.38 in 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	3	None identified	Based on a cutoff score of >3 or unspecified, sensitivity was 0.25 and 0.53 and specificity was 0.62 and 0.73 in 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	3	None identified	Based on a “high-risk” assessment, sensitivity was 0.73 and 0.83 and specificity was 0.43 and 0.88 in 2 studies, for positive likelihood ratios of 1.28 and 7.18 and negative

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of Evidence[b]	Other Factors	Estimates of Effect or Findings
							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	NA	NA	NA	Insufficient	NA	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	NA	NA	NA	Insufficient	NA	No evidence.
Comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids							
Outcomes related to abuse	None	NA	NA	NA	Insufficient	NA	No evidence.
Effects of Opioid Therapy for Acute Pain on Long-term Use (Key Question 5)							
Long-term opioid use	New for update: 2 cohort studies (n = 399 852)	Serious limitations	No inconsistency	No imprecision	3	None identified	One study found use of opioids within 7 d of low-risk surgery associated with increased likelihood of opioid use at 1 y, adjusted OR, 1,44 (95% Cl, 1.39–1.50).

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of Evidence[b]	Other Factors	Estimates of Effect or Findings
							One study found use of opioids within 15 d 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% Cl, 1,55–2.78) for 1–140 MM E/d and OR, 6.14 (95% Cl, 4.92–7.66) for ≥450 MM E/d.

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ER/LA, extended-release/long-acting; HR, hazard ratio; IRR, incidence rate ratio; KQ, key question; MME, morphine milligramequivalents; NA, not applicable (no evidence available for rating); OR, odds ratio.

[a]Ratings were made per GRADE quality assessment criteria; “no limitations” indicates that limitations assessed through the GRADE method were not identified. This table is an update and modification of data presented previously in an online AHRQ-sponsored report on the effectiveness and risks of long-term opioid treatment of chronic pain.[7]

[b]Types of evidence are described in Box 1.

Table 2.

Relationship Between Dose and Overdose

Source	Topic	Population	Primary Outcomes	Key Findings
Bohnert et al,[27] 2016[a]	Matched case-controlstudy examining association between opioid dosage and fatal overdose	VeteransHealth Administration patients with chronic pain receiving opioid therapy, 2004–2009	Unintentional fatalopioid overdose	24% of controls had dosages >50 MME/d, but 59% of cases had dosages above this level.
Bohnert et al,[22] 2011[a]	Case-cohort study examining the association between prescribed opioid dosage in MME/d and riskof opioid overdose death	VeteransHealth Administration patients receiving opioid therapy for pain, 2004–2005	Fatal opioid overdose	Among patients with chronic pain, receiving 20-<50 MME/d, 50-<100 MME/d, and ≥100 MME/d was associated with adjusted HRs for overdose death of 1.88, 4.63, and 7.18 comparedwith 1-<20 MME/d.
Dasgupta et al,[23] 2015[a]	Prospective observational cohort study investigating fatal overdose among patients receiving opioid pain medication	Residents of North Carolina receiving a prescription for opioid pain medication	Overdose death involving opioid pain medication	Overdose risk increased steadily in a dose-dependent manner; rate of increase decreased after 200 MME/d. Evidence of concurrent benzodiazepine prescription in the past year was 80%, and benzodiazepines were determined to be involved in 61% of deaths involving opioid pain medications.
Dunn et al,[19] 2010[b]	Cohort study examining rates ofopioid overdose and association with opioid dosage among patients receiving chronic opioid therapy	Health maintenance organization patients who received ≥3 opioid prescriptions within 90 d for chronic noncancer pain	Opioid-related overdose (fatalor nonfatal)	Compared with receiving 1-<20 MME/d, receiving 20-<50 MME/d, 50-<100 MME d, and >100 MME/d was associated with adjusted HRs for overdose of 1.4, 3.7, and 8.9.
Gomes et al,[20] 2011[b]	Case-control study examining association between opioid dose level and opioid-related mortality	Ontario residents aged 15–64y who received an opioid for nonmalignant pain through public prescription drug coverage, 1997–2006	Coroner's determination of opioid-related death	Compared with receiving 1-<20 MME/d, receiving 20–49 MME/d, 50–99 MME d, and 100–199 MME/d was associated with odds ratios for fatal overdose of 1.3,1.9, and 2.0.
Gwira Baumblatt et al,[24] 2014[a]	Matched case-control study examining association between opioid dosage or number ofprescribers or pharmacies with overdose death	Patients enrolled in Tennessee Controlled Substances Monitoring Program, 2007–2011	Fatal overdose	Opioid-related overdose death was associated with >100 MME/d, ≥4 prescribers, and ≥4 pharmacies (adjusted odds ratios, 11.2, 6.5, and 6.0). At least one of these risk factors was present in 55% of overdose deaths.
Liang and Turner, [25] 2015[a]	Longitudinal cohort study examining association between opioid dosage levels and overdose	Health maintenance program enrollees who filled at least 2 schedule II or III opioid analgesic prescriptions from January 2009 through July 2012	Fatal overdose	Overdose risk was associated with daily opioid dosage. In addition, among patients prescribed 50–100 MME/d, overdose risk was significantly greater for patients prescribed >1830 MME cumulatively over 6 mo.
Paulozzi et al,[21] 2012[a]	Matched case-control study examining association between overdose death and patterns of use ofopioid analgesics	New Mexico residents who died of unintentionaldrug overdoses and patients with prescriptions in the Prescription Monitoring Program, April 2006–March 2008	Fatal overdose	Patients receiving a dailyaverage dose of >40 MME had a 12.2 greater odds of overdose compared with those with lower opioid dosages or no opioid prescriptions.
Zedler et al,[26] 2014[a]	Association between opioid dose and overdose	Patients dispensed an opioid by the Veterans Health Administration, 2010–2012	Respiratory/central nervous system depression, overdose	Compared with patients with 1-<20 MME/d, the odds ratio of overdose was 1.5 for patients prescribed 20-<50 MME/d, 2.2 for patients prescribed 50-<100 MME/d, and 4.1 for patients prescribed ≥100 MME/d.

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

[a] Included in the contextual evidence review.

[b] Included in the clinical evidence review.

Table 3.

Effectiveness and Harms of Nonpharmacologic and Nonopioid Pharmacologic Treatments[a]

Source	Topic or Intervention	Participants or Population	Primary Outcomes	Key Findings	Study Quality
Busch et al,[48] 2007	Exercise training vs untreated control or nonexercise intervention	Systematic review of 33 RCTs with fibromyalgia patients	Global well-being, selected signs and symptoms, and physical function	Exercise training improves global well-being and physicalfunction. Supervised aerobic exercise training has beneficial effects on physical capacity and fibromyalgia symptoms.	Four studies were classified as high quality, 15 as moderate quality, and 14 as low quality
Chaparro et al,[49] 2014	Noninjectable opioids vs placebo or other treatments	Systematic review of 15 RCTs with patients with chronic low back pain	Pain	One trialfound tramadolsimilar to celecoxib for pain relief. Two trials did not find a difference between opioids and antidepressants for pain or function.	Low- to moderate-quality evidence
Collins et al,[50] 2000	Antidepressants vs placebo; anticonvulsants vs placebo	Systematic review of 19 RCTs for diabetic neuropathy or postherpetic neuralgia	Pain	For diabetic neuropathy, the NNT for ≥50% pain relief was3.4 for antidepressants (12 trials, 10 evaluated TCAs and 3 SSRIs) and 2.7 for anticonvulsants (3 trials). For postherpetic neuralgia, the NNT was 2.1 for antidepressants (3 studies evaluating TCAs) and 3.2 for anticonvulsants (1 study evaluating gabapentin).	The mean and median quality score for included studies was 4ona scale of 1–5
Fransen et al,[51] 2015	Exercise vs nonexercise group (active or no treatment)	Systematic review of 54 RCTs or quasi-randomized trials for knee osteoarthritis	Reduced joint pain or improved physical function and quality of life	Exercise reduced pain, improved function, and improved quality of life immediatelyaftertreatment; in studies providing posttreatment follow-up data, improved pain and function were sustained for 2–6 mo.	High-quality evidence for reduced pain and improved quality of life and moderate-quality evidence for improved function
Fransen et al,[52]2014	Exercise vs nonexercise group (active or no treatment)	Systematic review of 10 RCTs or quasi-randomized trials for hip osteoarthritis	Reduced joint pain and improved physical function and quality of life	Exercise reduced pain and improved function immediatelyafter treatment; in studies providing posttreatment follow-up data, improved pain and function were sustained for at least 3–6 mo.	High-quality evidence for reduced pain and improved function
Häuser et al,[53] 2013	Duloxetine vs placebo; milnacipran vs placebo	Systematic review of 10 RCTs for fibromyalgia patients	Benefits and harms	Duloxetine and milnacipran reduced pain bya smallamount compared with placebo.	Risk of bias in included studies was low
Hayden et al,[54] 2005	Exercise therapy vs no treatment, other conservative treatments	Systematic review consisting of 61 RCTs for low back pain	Pain, function	Exercise therapy reduces pain and improves function with small magnitudes of effect. Effectiveness of exercise therapy appears to be greater in populations visiting a health care provider compared with the generalpopulation.	Only a small number of studies rated as high quality; potential publication bias
Lee et al,[55] 2014	CIM therapies vs single self-care CIM, non-self-care CIM, usualcare/no treatment, other multimodalprogram, or other control	Systematic review of 26 RCTs for management of chronic pain	Pain symptoms	Integrative multimodal therapies resulted in positive, but sometimes mixed, effects on pain symptoms compared with active controls or single self-care modalities. More studies are needed to make strong conclusions about effectiveness.	Large majority of poor quality, including weaknesses in randomization and allocation concealment

Source	Topic or Intervention	Participants or Population	Primary Outcomes	Key Findings	Study Quality
Lunn etal,[56] 2014	Duloxetine vs placebo or other controls	Systematic review of 18 RCTs for neuropathic pain, chronic pain conditions without identified cause, or fibromyalgia	Benefits and harms of duloxetine	Duloxetine at 60 mg and 120 mg daily, but not lower dosages, were effective in reducing pain in diabetic peripheralneuropathy pain and in fibromyalgia.	Moderate-quality evidence for diabetic neuropathy; lower-quality evidence for fibromyalgia; some risk of bias
Moore et al,[57] 2009	Pregabalin vs placebo or any active control	Systematic review of 25 double-blind RCTs for postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain, or fibromyalgia	Analgesic efficacy and associated adverse events	Pregabalin was effective in patients with postherpetic neuralgia, diabetic neuropathy, central neuropathic pain, and fibromyalgia at doses of 300 mg, 450 mg, and 600 mg (but not at 150 mg) daily. NNTs were generally ≤6 for moderate benefit in postherpetic neuralgia and diabetic neuropathy but ≥7 for fibromyalgia.	Studies all had Oxford quality scores based on randomization, blinding, and reporting of dropout ≥3 (out of maximum of 5)
Moore et al,[58] 2014	Gabapentin vs placebo	Systematic review of 37 RCTs for neuropathic pain or fibromyalgia	Analgesic efficacy and adverse effects	Gabapentin was significantly more effective than placebo in reducing pain in diabetic neuropathyand postherpeticneuralgia. Evidence was insufficient for other conditions.	“Second-tier” evidence (some risk of bias, but adequate numbers in the trials)
Roelofs et al,[59] 2008	NSAIDs and COX-2 inhibitors vs control	Systematic review of 65 RCTs for nonspecific low back pain	Acute low back pain	NSAIDs are more effective than placebo for acute and chronic low back pain without sciatica, but have more adverse effects. NSAIDs are not more effective than acetaminophen but had more adverse effects. No type of NSAIDs, including COX-2 inhibitors, was found to be more effective than other NSAIDs.	Mixed high- and low-quality studies
Saarto et al,[60] 2010	Antidepressants vs placebo or other controls	Systematic review of 61 RCTs for neuropathic pain	Pain	TCAs and venlafaxine have low NNTs (3.6 and 3.1, respectively) for at least moderate pain relief.	Study quality limited byinsufficient reporting detail
Salerno et al,[61] 2002	Antidepressants vs placebo	Systematic review of 9 RCTs for chronic back pain	Back pain	Antidepressants were associated with small but significant improvement in pain severity; improvements in function were not significant. Most (6) studies evaluated TCAs.	Moderate-quality studies
Staiger et al,[62] 2003	Antidepressants vs placebo	Systematic review of 7 RCTs in patients with chronic low back pain	Back pain	Four of 5 studies evaluating TCA and tetracyclic antidepressants found significant improvement in chronic low back pain. Other antidepressants studied (2 studies evaluating SSRIs and 1 evaluating trazodone) did not show significant pain improvement.	Mixed quality (quality scores ranged from 11–19 out of 22)
Trelle et al,[63] 2011	NSAIDs vs other NSAIDs or placebo	Meta-analysis of 31 RCTs comparing any NSAID with other NSAID or placebo for any medical condition	Myocardial infarction, stroke, cardiovascular death, death from any cause	Compared with placebo, NSAIDs were associated with increased risk of myocardial infarction, stroke, and cardiovascular death.	Generally high
Welsch et al,[64] 2015	Opioids (including tramadol) vs nonopioids (including acetaminophen, NSAIDs/ COX-2 inhibitors, mexiletine,	Systematic review of 10 RCTs in patients with neuropathic pain, low back pain, or osteoarthritis	Efficacy (including various pain measures), tolerability, and safety	There was no significant difference between opioids and nonopioid analgesics in pain reduction; nonopioids were superior to opioids in improving physical function and	One study had a high, 2 studies a moderate, and 7 studies a low study quality

Source	Topic or Intervention	Participants or Population	Primary Outcomes	Key Findings	Study Quality
	anticonvulsants, antidepressants, and muscle relaxants)			were better tolerated. When patients from tramadol trials (n randomized = 2788) were removed from results of the review, results for pain and function for patients receiving opioids (morphine) compared with alternative drugs (n randomized = 223) had wide, overlapping confidence intervals. Improved tolerability foralternative drugs vs morphine remained significant.	
Wiffen et al,[65] 2014	Carbamazepine vs placebo or other active control	Systematic review consisting of 10 RCTs in adults with chronic neuropathic pain or fibromyalgia	Pain relief	Carbamazepine provided better pain relief than placebo for trigeminal neuralgia, diabetic neuropathy, and poststroke pain for ≤4 weeks. Dizziness and drowsiness were commonly reported with carbamazepine. In 4 studies, 65% of patients receiving carbamazepine vs 27% receiving placebo experienced ≥1 adverse event. In 8 studies, 3% of patients receiving carbamazepine withdrew because of adverse events (vs 0% taking placebo).	Third-tier evidence (trials involving small numbers of participants; considered likely to be biased, with outcomes of limited clinical utility, or both)
Williams et al,[66] 2012	Cognitive behavioral therapy or behavioral therapy	Systematic review of 42 RCTs for patients with nonmalignant chronic pain except headache	Pain, disability, mood, and catastrophic thinking	Cognitive behavioral therapy was found to have small to moderate effects on pain, disability, mood, and catastrophic thinking immediatelyafter treatment when compared with usual treatment or deferred cognitive behavioral therapy, but only effects on mood persisted at follow-up. Behavioral therapy had a positive effect on mood immediately after treatment.	Mean quality of study design, 15.8 out of 26 (SD 4.3; range, 9–24 out of 26)

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

[a] All the studies in this table were included in the contextual evidence review.

Table 4.

Morphine Milligram Equivalent Doses for Commonly Prescribed Opioids[a]

Opioid[b]	Conversion Factor
Codeine	0.15
Fentanyl transdermal, μg/h	2.4
Hydrocodone	1
Hydromorphone	4
Methadone, mg/d	
1–20	4
21–40	8
41–60	10
≥61–80	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Tapentadol[c]	0.4

[a] Adapted from Von Korff M, Saunders K, Ray GT, et al. *Clin J Pain*. 2008;24:521–527, and Interagency Guideline on Prescribing Opioids for Pain. Washington State Agency Medical Directors' Group. http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf. Accessed February 19, 2016.

[b] All doses are in mg/d except for fentanyl, which is μg/h. Multiply the daily dosage for each opioid by the conversion factor to determine the dose in morphine milligram equivalents (MME). For example, tablets containing hydrocodone, 5 mg, and acetaminophen, 300 mg, taken 4 times a day would contain a total of 20 mg of hydrocodone daily, equivalent to 20 MME daily; extended-release tablets containing oxycodone, 10 mg, and taken twice a day would contain a total of 20 mg of oxycodone daily, equivalent to 30 MME daily.

[c] Tapentadol is a μ-receptor agonist and norepinephrine reuptake inhibitor. Morphine milligram equivalents are based on degree of μ-receptor agonist activity, but it is unknown if this drug is associated with overdose in the same dose-dependent manner as observed with medications that are solely μ-receptor agonists.