CDC Clinical Practice Guideline for Prescribing Opioids–United States, 2022

Prepared by
Deborah Dowell, MD[1]
Kathleen R. Ragan, MSPH[1]
Christopher M. Jones, PharmD, DrPH[2]
Grant T. Baldwin, PhD[1]
Roger Chou, MD[3]

[1]Division of Overdose Prevention, National Center for Injury Prevention and Control, CDC, Atlanta, Georgia
[2]Office of the Director, National Center for Injury Prevention and Control, CDC Atlanta, Georgia
[3]Pacific Northwest Evidence-based Practice Center and Oregon Health & Science University, Portland, Oregon

CONTENTS

This clinical practice guideline is

- A clinical tool to improve communication between clinicians and patients and empower them to make informed, person-centered decisions related to pain care together
- Intended for primary care clinicians and other clinicians providing pain care for outpatients aged ≥18 years old with:
    - acute pain (duration <1 month);
    - subacute pain (duration of 1-3 months); or
    - chronic pain (duration of >3 months)
- Intended to be flexible to enable person-centered decision-making, taking into account an individual's expected health outcomes and well-being.

This clinical practice guideline is not

- A replacement for clinical judgment or individualized, person-centered care
- Intended to be applied as inflexible standards of care across patients, and/or patient populations by healthcare professionals, health systems, pharmacies, third-party payers, or governmental jurisdictions or to lead to the rapid tapering or discontinuation of opioids for patients
- A law, regulation, and/or policy that dictates clinical practice or a substitute for FDA-approved labeling
- Applicable to the following types of pain treatment:
    - sickle cell disease-related pain;
    - cancer pain;
    - palliative care; or
    - end-of-life care

Summary

This clinical practice guideline updates and expands the CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016 (Dowell, Haegerich, & Chou, 2016) and provides evidence-based recommendations for clinicians providing pain care, including those prescribing opioids, for outpatients aged ≥18 years with acute pain (duration <1 month), subacute (duration of 1-3 months) pain, or chronic (duration of >3 months) pain, and excluding of sickle cell disease-related pain management, cancer pain

treatment, palliative care, and end-of-life care. Content on use of opioids for acute pain and on tapering opioids for patients already receiving higher dosages for subacute or chronic pain has been substantially expanded. This update includes recommendations for primary care and other clinicians (including physicians, nurse practitioners, physician assistants, and oral health practitioners) managing pain in outpatient settings. Applicable settings include clinician offices, clinics, and urgent care centers. The recommendations do not apply to inpatient care received while hospitalized or to care received while in an emergency department or other observational setting from which a patient might be admitted to inpatient care but do apply to prescribing for pain management upon discharge (from emergency departments, hospitals, or other facilities).

This clinical practice guideline addresses:

1) Determining whether or not to initiate opioids for pain;

2) Opioid selection and dosage;

3) Opioid duration and follow-up; and

4) Assessing risk and addressing potential harms of opioid use.

CDC developed this clinical practice guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, and recommendations are made based on a systematic review of the available scientific evidence while considering benefits and harms, patients', caregivers', and clinicians' values and preferences, and resource allocation (e.g., costs to patients or health systems, including clinician time). As described in more detail below, CDC obtained input on this updated clinical practice guideline in a wide variety of avenues including conversations with patients, caregivers, and clinicians, through *Federal Register* notices and comments from the public, peer reviewers, and a federally chartered advisory committee.

The clinical evidence reviews found that nonopioid therapies are effective for many common types of acute pain and found insufficient evidence to determine long-term (>1 year) benefits of opioid therapy for chronic pain. Recommendations include that opioids should be used only when benefits for pain and function are expected to outweigh risks. Before starting opioids for subacute or chronic pain, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy, work with patients to establish treatment goals for pain and function and consider how opioid therapy will be discontinued if benefits do not outweigh risks. When opioids are initiated, clinicians should prescribe the lowest effective dosage of immediate-release opioids for no longer than needed for the expected duration of pain severe enough to require opioids. During ongoing opioid therapy, clinicians should collaborate with patients to evaluate and carefully weigh benefits and risks of continuing opioid therapy and exercise care when increasing, continuing, or reducing opioid dosage. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and should work with patients to incorporate relevant strategies to mitigate risk, including offering naloxone when factors that increase risk for opioid overdose are present, and reviewing potential interactions with any other prescribed medications or substances used. Clinicians should offer or arrange treatment with medication for patients with opioid use disorder.

It is imperative that people with pain receive the most appropriate and effective pain treatment with careful consideration of the benefits and risks of all treatment options. Clinicians should collaborate with patients when making treatment decisions and designing a treatment plan, including when initiating or changing pain management strategies and, particularly, when considering initiating, increasing, tapering, or discontinuing opioids. Clinicians should avoid abrupt discontinuation of opioids, especially for patients receiving high dosages of opioids, should avoid dismissing patients from care, and should ensure (provide or arrange) appropriate care for patients with pain and patients with

complications from opioid use (e.g., opioid use disorder). Special attention should be given to ensure high quality and equitable care across sociodemographic groups, for example, through linguistically tailored care and cost assistance programs to ensure access to appropriate pharmacotherapy, psychological support, and physical therapy as needed. This voluntary clinical practice guideline provides recommendations only and is intended to be flexible to support, not supplant, clinical judgment and individualized, person-centered decision-making. This clinical practice guideline should not be applied as inflexible standards of care across patient populations by healthcare professionals, health systems, pharmacies, third-party payers, or state, local, and federal organizations or entities.

This clinical practice guideline is intended to improve communication between clinicians and patients about the risks and benefits of pain treatment, including opioid therapy for pain, improve the safety and effectiveness of pain treatment, mitigate pain, and improve function and quality of life for patients with pain, and reduce risks associated with opioid therapy, including opioid use disorder, overdose, and death.

Introduction

Background

Pain is one of the most common reasons adults seek medical care in the United States (Schappert & Burt, 2006). Acute pain, a nearly universal experience, is a physiologic response to noxious stimuli that can become pathologic, is normally sudden in onset, time limited (<1 month), and often caused by injury, trauma, or medical treatments such as surgery (Institute of Medicine Committee on Advancing Pain Research Care and Education, 2011; Tighe et al., 2015). Chronic pain, defined in this clinical practice guideline as pain that typically lasts greater than three months or past the time of normal tissue healing, is often interlinked with acute pain (International Association for the Study of Pain, 1986). Chronic pain can be the result of an underlying medical disease or condition, injury, medical

treatment, inflammation, or an unknown cause (Institute of Medicine Committee on Advancing Pain Research Care and Education, 2011). It is estimated that approximately 1 in 5 U.S. adults had chronic pain in 2019, and approximately 1 in 14 adults experienced "high-impact" chronic pain, defined as having pain most days or every day in the past three months that limited life or work activities (Zelaya, Dahlhamer, Lucas, & Connor, 2020). Pain, especially chronic pain, can impact almost every aspect of an individual's life, leading to impaired physical functioning, poor mental health, and reduced quality of life, and contributes to substantial morbidity each year (U.S. Department of Health and Human Services, 2019b). In 2011, the economic costs of chronic pain were estimated to range from $560 to $635 billion in annual direct medical costs, lost productivity, and disability (Institute of Medicine Committee on Advancing Pain Research Care and Education, 2011).

Pain is a complex phenomenon that is influenced by multiple factors, including biological, psychological, and social factors (Chou et al., April 2020). Given this complexity, there is substantial heterogeneity in the effectiveness of various pain treatments depending on the type of underlying pain or condition being treated (Chou et al., April 2020; Chou et al., December 2020; Halker Singh et al., December 2020; McDonagh et al., April 2020; Skelly et al., April 2020). Patients may experience persistent pain that is not well controlled (U.S. Department of Health and Human Services, 2019b). In addition, chronic pain often co-occurs with behavioral health conditions, including mental and substance use disorders (Hooten, 2016; Morasco et al., 2011); suicidal ideation also is common among patients with chronic pain (Racine, 2018; M. T. Smith, Edwards, Robinson, & Dworkin, 2004). Data from death investigations in 18 states between 2003 and 2014 indicate that at least 9% of suicide decedents had evidence of having chronic pain at the time of their death, although this is likely an underestimate given limitations of the underlying data sources used in the study (Petrosky et al., 2018). These factors and potentially deleterious outcomes associated with chronic pain for some individuals add to the clinical complexity and underscore the importance of adequately treating and caring for people with pain. Thus,

prevention, assessment, and treatment of pain is a persistent challenge for clinicians. Pain may go unrecognized, and some individuals — in particular members of some marginalized racial and ethnic groups, women, older persons, people with cognitive impairment, individuals with mental and substance use disorders, and individuals with cancer and at the end-of-life or those with sickle cell disease — can be at risk for inadequate pain treatment (Bazargan, Yazdanshenas, Gordon, & Orum, 2016; Becker et al., 2017; C Evans, Bazargan, Cobb, & Assari, 2019; Institute of Medicine Committee on Advancing Pain Research Care and Education, 2011; Rupp & Delaney, 2004; Simon, Snow, & Wakeman, 2020; U.S. Department of Health and Human Services, 2019b; Yazdanshenas et al., 2016).

While there is significant opportunity for improvement in pain management broadly across the United States, data underline particular opportunities for attending to specific, long-standing health disparities (Joynt et al., 2013; Ly, 2019; Morden, Chyn, Wood, & Meara, 2021) in the treatment of pain. For example, patients who identify as Black, Latino, and Asian have been found to receive fewer postpartum pain assessments relative to White patients (Bazargan et al., 2016; C Evans et al., 2019; J. D. Johnson et al., 2019; Rupp & Delaney, 2004; Simon et al., 2020; Yazdanshenas et al., 2016). Black (Goyal, Kuppermann, Cleary, Teach, & Chamberlain, 2015; P. Lee et al., 2019) and Latino (P. Lee et al., 2019) patients are less likely to receive analgesia for acute pain. Among Black and White patients receiving opioids for pain, Black patients are less likely to be referred to a pain specialist and receive prescription opioids at lower dosages than White patients (Hausmann, Gao, Lee, & Kwoh, 2013; Morden et al., 2021). Racial/ethnic differences remain even after adjusting for access-related factors, as well as the needs and preferences of patients, and the appropriateness of the intervention (Ly, 2019). These disparities appear to be further magnified if patients from some racial and ethnic groups reside in socioeconomically disadvantaged neighborhoods (Joynt et al., 2013). Women may be at higher risk for inadequate pain management (Majedi et al., 2019) although they have higher opioid prescription fill rates (Schieber, Guy, Seth, & Losby, 2020) than men at a population level. In addition, geographic disparities contribute to

increased use of opioids for conditions for which nonopioid treatment options may be preferred but may be less available. For example, compared to adults living in nonrural areas, adults living in rural areas are significantly more likely to be prescribed opioids for chronic nonmalignant pain (Prunuske et al., 2014). Despite the fact that American Indian/Alaska Native, non-Hispanic and White, non-Hispanic populations have experienced much higher rates of prescription opioid-related overdose deaths than Black, non-Hispanic, Hispanic, or Asian/Pacific Islander, non-Hispanic populations (Wilson, Kariisa, Seth, Smith IV, & Davis, 2020), there is evidence that application of safeguards in opioid prescribing are disproportionately applied to Black patients. Black patients in one study were more likely than White patients to receive regular office visits and have restricted early refills (Becker et al., 2011), and clinicians in another study were substantially more likely to discontinue opioids given evidence of misuse when patients were Black compared to when patients were White (Gaither et al., 2018). Pain being differentially untreated or undertreated as a result of clinician biases persists and demands immediate and sustained attention and action (Ghoshal, Shapiro, Todd, & Schatman, 2020; Nelson & Hackman, 2013; Pletcher, Kertesz, Kohn, & Gonzales, 2008; Soares, Knowles, & Friedmann, 2019).

Given the clinical, psychological, and social consequences associated with pain including limitations in activities, lost work productivity, reduced quality of life, and pervasive stigma, it is essential that clinicians have the training, education, guidance, and resources to provide appropriate, holistic, and compassionate care for patients with pain (Institute of Medicine Committee on Advancing Pain Research Care and Education, 2011; U.S. Department of Health and Human Services, 2019b). A key aim of pain management is the provision of person-centered care, including the proper evaluation to establish a diagnosis, with measurable outcomes that focus on optimizing function and quality of life, that is built on a foundation of trust between patients and clinicians (U.S. Department of Health and Human Services, 2019b). To achieve this aim, it is important that clinicians consider the full range of pharmacological and nonpharmacological treatments for pain care, and health systems, payers, and

governmental programs and entities make the full spectrum of evidence-based treatments accessible to patients with pain and their treating clinicians.

The range of therapeutic options that might benefit patients has historically been inaccessible to many due to a variety of factors, including inadequate clinician education, training, and guidance, unconscious bias, a shortage of pain management specialists, insufficient access to treatment modalities such as behavioral therapy, siloed health systems, insurance coverage and reimbursement policies, and lack of clarity around the evidence supporting different pain treatments (Becker et al., 2017; Benzing, Bell, Derazin, Mack, & MacIntosh, 2020; Heyward et al., 2018; Jamison, Sheehan, Scanlan, Matthews, & Ross, 2014; D. H. Lin et al., 2018; Sabin & Greenwald, 2012; Saluja & Bryant, 2021; U.S. Department of Health and Human Services, 2019b). In part due to these factors affecting access to a wide range of treatment modalities, for many years, medications such as prescription opioids have been the mainstay to treat pain, despite very limited evidence to support their long-term (> 1 year) benefits, with most placebo-controlled trials shorter than 6 weeks in duration (Chou et al., September 2014; Dahlhamer, Connor, Bose, Lucas, & Zelaya, 2021; Institute of Medicine Committee on Advancing Pain Research Care and Education, 2011; U.S. Department of Health and Human Services, 2019b).

While opioids can be essential medications for the management of pain, they carry significant potential risk. A systematic review published in 2014 by the Agency for Healthcare Research and Quality (AHRQ) found insufficient evidence to demonstrate long-term benefits of prescription opioid treatment for chronic pain, and also that long-term prescription opioid use was associated with increased risk of overdose and opioid misuse, among other risks, with some, such as overdose, being dose dependent (Chou et al., September 2014). Based on accumulating evidence of potential risks for patients, in 2014 the U.S. Food and Drug Administration (FDA) required new safety labeling changes for extended-release and long-acting opioids to include a boxed warning on the risks of addiction, abuse, and misuse which can potentially lead to overdose and death, as well as the risk for neonatal opioid withdrawal syndrome

among patients receiving opioids during pregnancy (U.S. Food and Drug Administration, 2014a). These warnings were subsequently added to the labels for immediate-release opioids in 2016 (U.S. Food and Drug Administration, 2016).

In addition to the potential risks for patients prescribed opioids, these medications carry risks due to their potential for diversion and nonmedical use among individuals to whom they were not prescribed (Substance Abuse and Mental Health Services Administration, 2021a). In the United States, opioid prescribing increased four-fold between 1999 and 2010, and this increase was paralleled by a nearly four-fold increase in overdose deaths involving prescription opioids during the same time period (Paulozzi, Jones, Mack, & Rudd, 2011) as well as increases in prescription opioid use disorder (Han, Compton, Jones, & Cai, 2015). In addition to the overall volume of opioid prescriptions increasing during this period, how opioids were prescribed also changed, with opioids increasingly prescribed at higher dosages and for longer durations — prescribing behaviors associated with opioid use disorder and overdose (Bohnert et al., 2011; Edlund et al., 2014). Thus, the limited evidence of long-term effectiveness of opioids for chronic pain coupled with risks for patients and for people using prescription opioids that were not prescribed to them underscored the importance of reducing inappropriate opioid prescribing, while at the same time advancing evidence-based pain care to improve the lives of people living with pain.

Recognizing the need for a national guideline on pain management that could improve appropriate opioid prescribing while minimizing opioid-related risks, CDC released the CDC Guideline for Prescribing Opioids for Chronic Pain in 2016 (referred to as the 2016 CDC Guideline hereafter). The 2016 CDC Guideline included 12 recommendations for the prescribing of opioids by primary care clinicians for chronic pain in outpatient settings outside of active cancer treatment, palliative care, and end-of-life care (Dowell et al., 2016). The recommendations in the 2016 CDC Guideline were based on a systematic review of the best available evidence at the time, along with input from experts and from the public,

and review and deliberation by a federally chartered advisory committee. The ultimate goal of the 2016 CDC Guideline was: 1) to ensure that clinicians and patients considered safer and more effective pain treatment, 2) improve patient outcomes such as reduced pain and improved function, and 3) reduce the number of persons who developed opioid use disorder, overdose, or experienced other prescription opioid-related adverse events (Dowell et al., 2016). To facilitate uptake of the 2016 CDC Guideline into clinical practice, CDC employed a broad-reaching implementation strategy that included clinician education and training, partnerships with health systems and payers, and multiple clinical tools and fact sheets (Centers for Disease Control and Prevention, 2021b).

While the number of overall opioid prescriptions in the United States had been declining since 2012, the release of the 2016 CDC Guideline furthered these declines. The timing of its release was associated with accelerated decreases in overall opioid prescribing and declines in high-risk prescribing behaviors cautioned against in the 2016 CDC Guideline, such as high-dose opioid prescribing and the concurrent prescribing of opioids and benzodiazepines (Bohnert, Guy, & Losby, 2018). Though not the intent of the 2016 CDC Guideline, design and implementation of new laws, regulations, and policies also drew from its recommendations. As one example since 2016, consistent with SUPPORT ACT requirements, many state Medicaid programs have used the guideline as well as other resources in creating opioid edits in their pharmacy programs (Centers for Medicare and Medicaid Services, 2019). More than half of all states have passed legislation that limits initial opioid prescriptions for acute pain to a seven day supply or less (National Conference of State Legislatures, June 30, 2019.), and many insurers, pharmacy benefit managers, and pharmacies also have enacted similar policies (U.S. Department of Health and Human Services, 2020). In addition, at least 17 states have passed laws that require the co-prescription of naloxone when risk factors such as high doses of opioids or concomitant opioids and benzodiazepines are prescribed (Haffajee, Cherney, & Smart, 2020).

While some laws, regulations, and policies that were derived from the 2016 CDC Guideline might have had positive results for some patients, a central tenet of the 2016 CDC Guideline was that the recommendations are voluntary and are intended to be flexible to support, not supplant, individualized, patient-centered care. Of particular concern, some policies that were purportedly drawn from the 2016 CDC Guideline have, in fact, been notably inconsistent with the 2016 CDC Guideline and have gone well beyond its clinical recommendations (Dowell, Haegerich, & Chou, 2019; Kroenke et al., 2019; U.S. Department of Health and Human Services, 2019b). Such misapplication includes extension of the 2016 CDC Guideline to patient populations not covered in the 2016 CDC Guideline (e.g., cancer and palliative care), opioid tapers and abrupt discontinuation without collaboration with patients, rigid application of opioid dosage thresholds, application of the Guideline's recommendations for opioid use for pain to medications for opioid use disorder treatment (previously referred to as medication assisted treatment), duration limits by insurers and by pharmacies, and patient dismissal and abandonment (Dowell, Haegerich, et al., 2019; Kroenke et al., 2019; U.S. Food and Drug Administration, 2019c). These actions are not consistent with the 2016 CDC Guideline and have contributed to patient harm, including untreated and undertreated pain, serious withdrawal symptoms, worsening pain outcomes, psychological distress, overdose, and suicidal ideation and behavior (Coffin et al., 2020; Demidenko et al., 2017; Dowell, Haegerich, et al., 2019; Kroenke et al., 2019; Mark & Parish, 2019; U.S. Food and Drug Administration, 2019c).

Rationale

New evidence on the risks and benefits of prescription opioids for both acute and chronic pain, comparisons with nonopioid pain treatments, dosing strategies, opioid dose-response relationships, risk mitigation strategies, and opioid tapering and discontinuation has emerged since release of the 2016 CDC Guideline (Chou et al., April 2020; Chou et al., December 2020; Halker Singh et al., December 2020;

McDonagh et al., April 2020; Skelly et al., April 2020). In particular, studies have been published on misapplication of the 2016 CDC Guideline (Kroenke et al., 2019); benefits and risks of different tapering strategies and rapid tapering associated with patient harm (K. S. Gordon et al., 2020; James et al., 2019; Mark & Parish, 2019; U.S. Food and Drug Administration, 2019c); challenges in patient access to opioids (U.S. Department of Health and Human Services, 2019b); patient abandonment and abrupt discontinuation of opioids (U.S. Department of Health and Human Services, 2019b); a seminal randomized clinical trial comparing prescription opioids to nonopioid medications on long-term pain outcomes (E. E. Krebs et al., 2018); the association of characteristics of initial opioid prescriptions with subsequent likelihood for long-term opioid use (Deyo et al., 2017; Shah, Hayes, & Martin, 2017); and that many patients use a small proportion of opioids prescribed to them for postoperative pain (Hill, McMahon, Stucke, & Barth, 2017; Hill, Stucke, McMahon, Beeman, & Barth, 2018; Howard, Waljee, Brummett, Englesbe, & Lee, 2018).

Opioid prescribing has been declining since 2012, with the decline sharply accelerated after release of the 2016 CDC Guideline; however, these medications remain a common treatment for pain. In 2015-2018, approximately 6% of U.S. adults reported use of one or more prescription opioids in the past 30 days (Hales, Martin, & Gu, 2020), and in 2020, approximately 143 million opioid prescriptions were dispensed from pharmacies in the United States(Centers for Disease Control and Prevention, 2021c). In addition, rates of opioid prescribing continue to vary across states, medical specialties, patient demographics, and pain conditions in ways that cannot be explained by the underlying health status of the population and are often discordant with the 2016 CDC Guideline recommendations (Guy & Zhang, 2018; Hill et al., 2017; Ly, 2019; Mikosz et al., 2020; Schieber et al., 2019). The prevalence of prescription opioid misuse and opioid use disorder has also declined in recent years. Among people 12 and older in the U.S. in 2019, 9.7 million reported misuse of prescription opioids in the past year (decreased from 12.5 million in 2015), and 1.4 million met criteria for a past-year prescription opioid use disorder

(decreased from 2.0 million in 2015) (Substance Abuse and Mental Health Services Administration, 2020); however, prescription opioids remain the most commonly misused prescription drug in the United States in 2020 (Substance Abuse and Mental Health Services Administration, 2021a). Also in 2020, it is important to note that among those reporting misuse in the past year, 64.6% reported the main reason for their most recent misuse was to "relieve physical pain" compared to 11.3% to "feel good or get high" and 2.3% "because I am hooked or have to have it" (Substance Abuse and Mental Health Services Administration, 2021a). Taken together, these factors underscore the need for an updated clinical practice guideline on appropriate opioid prescribing and pain management.

This clinical practice guideline expands and updates the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain to provide evidence-based recommendations for the prescribing of opioid pain medication for acute, subacute, and chronic pain by clinicians for outpatients aged ≥18 years outside of sickle cell disease-related pain management, cancer pain treatment, palliative care, and end-of-life care. This clinical practice guideline update leverages new data to expand content on prescription opioids for acute and subacute pain throughout the recommendations. Importantly, the update also aims to clearly delineate recommendations that apply to patients who are being considered for initial treatment with prescription opioids and those who have already been receiving opioids as part of their ongoing pain management treatment. CDC developed a draft clinical practice guideline based on five systematic reviews of the best available evidence on the benefits and risks of prescription opioids, nonopioid pharmacological treatments, and nonpharmacological treatments. As described in more detail below, the draft clinical practice guideline was reviewed by an independent Federal Advisory Committee (CDC's Board of Scientific Counselors of the National Center for Injury Prevention and Control), peer reviewers, and the public, and revised by CDC based on feedback from these reviews. In addition, insights from patients, caregivers, and clinicians via conversations held in 2020 were incorporated during the clinical practice guideline update.

This clinical practice guideline provides recommendations only. It does not replace clinical judgment and individualized, patient-centered decision-making. The recommendations are based on emerging evidence, including observational studies or randomized clinical trials with notable limitations, and thus, when providing care, they should be considered in the context of the individual clinician-patient relationship based on a shared understanding and a "whole-person approach" that considers such factors as the patient's physical and psychological functioning, support needs, expected health outcomes and well-being, home environment, and home and work responsibilities. Flexibility for clinicians and patients is paramount when making clinical treatment decisions based on individual factors. The clinical practice guideline recommendations aim to improve communication between clinicians and patients about the risks and benefits of prescription opioids and other pain treatment strategies, improve the safety and effectiveness of pain treatment, improve pain, function, and quality of life for people with pain, and reduce the risks associated with opioid pain treatment (including opioid use disorder, overdose, and death) and with other pain treatment. Of utmost importance, this clinical practice guideline provides voluntary clinical practice recommendations for clinicians that should not be used as inflexible standards of care. The clinical practice guideline recommendations are also not intended to be implemented as absolute limits of policy or practice across populations by organizations, healthcare systems, or government entities.

Scope and audience

This clinical practice guideline is intended for clinicians who are treating outpatients aged ≥18 years with acute (duration <1 month) pain, subacute (duration of 1-3 months) pain, or chronic (duration of >3 months) pain outside of sickle cell disease-related pain management, cancer treatment, palliative care, and end-of-life care. For the purposes of this clinical practice guideline, "clinicians" refers to physicians, nurse practitioners, physician assistants, and oral health

practitioners. This clinical practice guideline update includes recommendations for primary care (e.g., internists, family physicians) and other (e.g., surgeons, emergency clinicians, occupational medicine and physical medicine and rehabilitation clinicians, neurologists) clinicians (including physicians, nurse practitioners, physician assistants, and oral health practitioners managing pain in outpatient settings. Applicable settings include clinician offices, clinics, and urgent care centers. The recommendations do not apply to inpatient care received while hospitalized or to care received while in an emergency department or other observational setting from which a patient might be admitted to inpatient care but do apply to prescribing for pain management upon discharge (from emergency departments, hospitals, or other facilities). As clinicians may work within team-based care, the recommendations refer to and promote integrated pain management and collaborative working relationships with, for example, behavioral health specialists, such as social workers or psychologists, and pharmacists.

In addition to updating recommendations based on new evidence regarding management of chronic pain, this clinical practice guideline update is meant to assist clinicians in weighing benefits and risks of prescribing opioid pain medication for painful acute conditions (e.g., low back pain, neck pain, other musculoskeletal pain, neuropathic pain, dental pain, pain due to kidney stones, and acute episodic migraines) and pain related to procedures (e.g., postoperative pain, pain from oral surgery). Several of these indications were prioritized in 2020 by an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (National Academies of Sciences Engineering and Medicine, 2020) as those for which evidence-based clinical practice guidelines would help inform prescribing practices, with the greatest potential impact on public health. The clinical practice guideline has additionally been updated to include content on management of subacute painful conditions — when duration falls between that typically considered acute (defined as <1 month in this clinical practice guideline) and chronic (generally considered as >3 months). Note that the durations used to define acute, subacute, and chronic pain might imply more specificity than is found in real-life patient experience, when pain

often gradually transitions from acute to chronic pain. These time-bound definitions are not meant to be absolute, but instead to provide approximate guides to facilitate consideration and practical use of recommendations by clinicians and patients.

The 2016 CDC Guideline for Prescribing Opioids for Chronic Pain focused on recommendations for primary care physicians. This clinical practice guideline expands the scope of the 2016 CDC Guideline to additional clinicians. While primary care physicians prescribe approximately 37% of all opioid prescriptions, other clinicians, including pain medicine clinicians (8.9%) and dentists (8.6%), account for significant proportions of prescriptions. Pain medicine and physical medicine and rehabilitation clinicians prescribe opioids at the highest rates, followed by orthopedic and family medicine clinicians (Guy & Zhang, 2018). Thus, expanding the clinical practice guideline's scope to outpatient opioid prescribing can provide evidence-based advice for many additional clinicians, including dentists and other oral health providers, clinicians managing postoperative pain in outpatients, and clinicians providing pain management for patients being discharged from emergency departments.

Many principles of pain management are similar whether or not the treating clinician is a pain management specialist, and many of the recommendations might be relevant for pain management specialists. In addition, many pain management specialists already follow principles outlined in this clinical practice guideline. However, use by pain management specialists is not the focus of this clinical practice guideline. Pain management specialists often have extensive training and expertise in pain management modalities that other clinicians do not, and they might see patients with clinical situations that are more complex, less prevalent, and not well-addressed by the available evidence; thus, the balance of benefits and risks to patients might differ when the treating clinician is a pain management specialist treating patients with complex pain conditions.

In addition, the recommendations address the use of opioid pain medication in certain special populations (e.g., older adults and pregnant people) and in populations with conditions posing special risks (e.g., a history of substance use disorder). The recommendations do not address the use of opioid pain medication in children or adolescents aged <18 years. The available evidence concerning the benefits and risks of long-term opioid therapy in children and adolescents remains limited, and few opioid medications provide information in the labeling regarding safety and effectiveness in pediatric patients. Guidelines and recommendations are available for pain management in children with sickle cell disease (Brandow et al., 2020) and undergoing surgical procedures (Michigan Opioid Prescribing Engagement Network), and for palliative care in adolescent and young adult patients with cancer (National Comprehensive Cancer Network).

While some principles in this clinical practice guideline might be helpful in the management of pain in sickle cell disease, cancer, palliative care, and end-of-life care, some recommendations might not be relevant for patients with these conditions and receiving care in these settings. Thus, this clinical practice guideline does not apply to patients experiencing pain associated with these conditions or settings. Other guidelines more specifically address pain management for patients with these conditions (Brandow et al., 2020; Denlinger, Sanft, & Armenian; National Comprehensive Cancer Network; Paice et al., 2016; Swarm et al., 2019). This does not imply that any other types of pain are more or less worthy of effective treatment – only that they are not covered by this clinical practice guideline. This clinical practice guideline follows the Institute of Medicine's definition of palliative care as care that provides relief from pain and other symptoms, supports quality of life, and is focused on patients with serious advanced illness (Committee on Approaching Death: Addressing Key End of Life Issues & Institute of Medicine, 2015). Palliative care can begin early in the course of treatment for any serious illness that requires advanced management of pain or other distressing symptoms (Committee on Approaching Death: Addressing Key End of Life Issues & Institute of Medicine, 2015). End-of-life care is defined as

410 care for persons in hospice care and others with a terminal illness or at high risk of dying in the near
411 future in hospitals, receiving long-term services and supports (including institutional care, and home and
412 community-based services), or at home. This clinical practice guideline does not apply to patients
413 undergoing cancer treatment, palliative care, or end-of-life care because of the unique therapeutic
414 goals, ethical considerations, opportunities for medical supervision, and balance of risks and benefits
415 with opioid therapy in such care. Readers are referred to the National Comprehensive Cancer Network
416 (NCCN) Clinical Practice Guidelines in Oncology: Adult Cancer Pain (Swarm et al., 2019), NCCN Clinical
417 Practice Guidelines in Oncology: Survivorship (Denlinger et al.), and Management of Chronic Pain in
418 Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline (Paice et al.,
419 2016) for recommendations on pain management for patients with cancer and patients who have
420 survived cancer. In addition, given unique considerations in management of pain related to sickle cell
421 disease, which can change the balance of benefits and risks for the use of opioids, clinicians should refer
422 to specific guidelines for pain management for patients facing painful complications of sickle cell disease
423 and are referred to the American Society of Hematology 2020 Guidelines for Sickle Cell Disease:
424 Management of Acute and Chronic pain (Brandow et al., 2020). In 2018, the National Comprehensive
425 Cancer Network and the American Society of Clinical Oncology convened and led a meeting including
426 representatives and guideline authors from the National Comprehensive Cancer Network, American
427 Society of Clinical Oncology, American Society of Hematology, and Centers for Disease Control and
428 Prevention to review existing pain management guidelines (Denlinger et al.; Dowell et al., 2016; Paice et
429 al., 2016; Swarm et al., 2019) and guidelines then in development (Brandow et al., 2020) from these
430 organizations. Meeting participants noted that these guidelines applied to different patient populations
431 and target audiences, but found no disagreement among recommendations when applied to the
432 appropriate patient and clinical situation (Schatz et al., 2020).

While this clinical practice guideline update includes content on pain management for patients with opioid use disorder, and one recommendation focuses on management of opioid use disorder as a complication of opioid use, recommendations on opioids used specifically as medications for opioid use disorder are not the focus of this clinical practice guideline. Readers are referred to *The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update* (American Society of Addiction Medicine, 2020) for more detailed recommendations on management of patients with opioid use disorder.

Methods for clinical practice guideline development

Methods for conducting systematic reviews

Sources of evidence

The 2016 CDC Guideline was based on a systematic clinical evidence review sponsored by AHRQ on the effectiveness and risks of long-term opioid therapy for chronic pain (Chou et al., September 2014; Chou et al., 2015), supplemented by a CDC update to the AHRQ-sponsored review and additional contextual questions (Dowell et al., 2016). The AHRQ-sponsored systematic review addressed the effectiveness of long-term opioid therapy for outcomes related to pain, function, and quality of life; the comparative effectiveness of different methods for initiating and titrating opioids; the harms and adverse events associated with opioids; and the accuracy of risk-prediction instruments and effectiveness of risk mitigation strategies on outcomes related to overdose, opioid use disorder, illicit drug use, and/or prescription opioid misuse. The CDC update to the AHRQ-sponsored review included more recently published literature (published during or after 2015) and an additional question on the association between opioid therapy for acute pain and long-term use. The contextual evidence review addressed effectiveness of nonpharmacologic and nonopioid pharmacologic treatments, clinician and patient values and preferences, and information regarding resource allocation.

For this CDC update to the 2016 CDC Guideline, CDC funded AHRQ in 2018 and 2019 to conduct five systematic reviews (Chou et al., April 2020; Chou et al., December 2020; Halker Singh et al., December 2020; McDonagh et al., April 2020; Skelly et al., April 2020). AHRQ's Evidence-based Practice Centers completed these reviews, which include new evidence related to the treatment of chronic and acute pain. The AHRQ review of opioids for chronic pain updated the evidence addressed in the prior (2016) CDC review and expanded upon it, by including studies on shorter term (1 to 12 month) outcomes of therapy involving opioids, effects of opioid plus nonopioid combination therapy, effects of tramadol, effects of naloxone co-prescription, risks of co-prescribed benzodiazepines, risks of co-prescribed gabapentinoids, and effects of concurrent use of cannabis (Chou et al., April 2020). The systematic clinical evidence review on opioids for chronic pain (Chou et al., April 2020) also included Contextual Questions on clinician and patient values and preferences and costs and cost-effectiveness of opioid therapy and risk mitigation strategies. In addition, CDC used four new, complementary AHRQ reviews on the benefits and harms of nonpharmacologic treatments for chronic pain (Skelly et al., April 2020), nonopioid pharmacologic treatments for chronic pain (McDonagh et al., April 2020), treatments for acute episodic migraine (Halker Singh et al., December 2020), and treatment for acute (non-migraine) pain (Chou et al., December 2020). A question on management of acute pain in the 2016 CDC review on opioids for chronic pain was moved to the new review on therapies for acute pain (Chou et al., December 2020). CDC also reviewed AHRQ-sponsored surveillance reports conducted in follow-up to the five systematic reviews for any new evidence that could potentially change systematic review conclusions (Chou R et al., 2022). To supplement the clinical evidence reviews, CDC sponsored a contextual evidence review on clinician and patient values and preferences and resource allocation (costs) for the areas addressed in the four new reviews (Chou et al., December 2020; Halker Singh et al., December 2020; McDonagh et al., April 2020; Skelly et al., April 2020).

Primary clinical questions guiding the systematic reviews

Across reviews, the main outcomes were pain, function, and quality of life. Harms varied depending on the therapy evaluated but included serious adverse events when reported; for opioids, key harms included overdose and harms related to opioid use disorder. The reviews of therapies for chronic pain assessed outcomes at short- (1 to <6 months), intermediate- (6 to <12 months), and long-term follow-up (≥12 months). The reviews of therapies for acute pain assessed outcomes at < 1 day; 1 day to <1 week; 1 week to <2 weeks; and 2 weeks to 4 weeks; the review of treatments for acute non-migraine pain also evaluated outcomes at ≥4 weeks. All reviews included key questions (KQs) or sub-questions on how benefits and harms varied according to demographic (age, sex, race), clinical (severity and duration of pain, medical and psychiatric comorbidities, concomitant medications), and intervention (dose, duration, intensity) characteristics.

The systematic clinical evidence reviews addressed questions in the following topic areas (details including questions available in the full AHRQ reports [Chou et al., April 2020; Chou et al., December 2020; Halker Singh et al., December 2020; McDonagh et al., April 2020; Skelly et al., April 2020]):

Opioids for chronic pain

- The effectiveness and comparative effectiveness (benefits, [KQ] 1 and harms, [KQ 2]) of long-term opioid therapy versus placebo, no opioid therapy, or nonopioid therapy.
- The comparative effectiveness of various opioid dosing strategies (KQ3):
    - Different methods for initiating and titrating opioids
    - Short-acting versus long-acting/extended-release opioids
    - Different long-acting opioids
    - Short- plus long-acting versus long-acting opioid alone

- Scheduled, continuous versus as-needed dosing
- Opioid dose escalation versus dose maintenance or use of dose thresholds
- Opioid rotation versus maintenance
- Different strategies for treating acute exacerbations of chronic pain
- Decreasing opioid doses or tapering off opioids versus continuation of opioids
- Different tapering protocols and strategies
- Different opioid dosages and durations of therapy

- The accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse; the effectiveness of risk prediction instruments; the effectiveness of various risk mitigation strategies; and comparative effectiveness of strategies for managing patients with opioid use disorder (KQ 4). The risk mitigation strategies are:
  - Opioid management plans
  - Patient education
  - Urine drug screening
  - Use of prescription drug monitoring program (PDMP) data
  - Use of monitoring instruments in patients prescribed opioids
  - More frequent monitoring intervals
  - Pill counts
  - Use of abuse-deterrent formulations

- Consultation with mental health specialists when mental health conditions are present or suspected
- Avoidance of co-prescribing of sedative hypnotics
- Co-prescribing of naloxone

Noninvasive nonpharmacological treatments for chronic pain

- The effectiveness and comparative effectiveness (benefits and harms) of noninvasive nonpharmacological treatments (exercise, mind-body practices, psychological interventions, multidisciplinary rehabilitation, mindfulness practices, musculoskeletal manipulation, physical modalities, and acupuncture) versus inactive treatments, usual care, no treatment, pharmacological therapy, or selected active treatments (exercise [chronic pain conditions other than headache] or biofeedback [headache]), for the following conditions:
  - Chronic low back pain (KQ 1)
  - Chronic neck pain (KQ 2)
  - Osteoarthritis (knee, hip, hand) (KQ 3)
  - Fibromyalgia (KQ 4)
  - Chronic tension headache (KQ 5)

Nonopioid pharmacologic treatments for chronic pain

- Effectiveness and comparative effectiveness (benefits [KQ 1] and harms [KQ 2]) of nonopioid pharmacologic agents (non-steroidal anti-inflammatory drugs [NSAIDs], antidepressants, anticonvulsants, acetaminophen, muscle relaxants, memantine, topical agents, and cannabis) versus placebo or other nonopioid pharmacologic agents.

Treatments for acute pain

- Effectiveness and comparative effectiveness (benefits and harms) of opioid therapy versus nonopioid pharmacologic therapy (acetaminophen, NSAIDs, skeletal muscle relaxants, benzodiazepines, antidepressants, anticonvulsants, cannabis) or nonpharmacologic therapy (exercise, cognitive behavioral therapy, meditation, relaxation, music therapy, virtual reality, acupuncture, massage, manipulation/mobilization, physical modalities); nonopioid pharmacologic therapy versus other nonopioid pharmacologic treatments or nonpharmacologic therapy; and nonpharmacologic therapy versus inactive treatments or usual care, for the following conditions:
    - Acute back pain (including back pain with radiculopathy) (KQ 1)
    - Acute neck pain (including neck pain with radiculopathy) (KQ 2)
    - Musculoskeletal pain not otherwise included in KQ 1 or KQ 2 (including fractures) (KQ 3)
    - Peripheral neuropathic pain (related to herpes zoster and trigeminal neuralgia) (KQ 4)
    - Postoperative pain (excluding inpatient management of pain following major surgical procedures (KQ 5)
    - Dental pain (KQ 6)
    - Kidney stones (including inpatient management) (KQ 7)
    - Sickle cell crisis (episodic pain) (KQ 8)

Treatments for acute episodic migraine

- Effectiveness and comparative effectiveness (benefits and harms) of:

- Opioid therapy versus nonopioid pharmacologic therapy (acetaminophen, NSAIDs, triptans, ergot alkaloids, combination analgesics, muscle relaxants, anti-nausea medications, cannabis, or others [e.g., gepants]) or nonpharmacologic therapy (exercise, cognitive behavioral therapy, acupuncture, or others) (KQ 1)
- Nonopioid pharmacologic therapy versus a different nonopioid pharmacologic therapy or nonpharmacologic therapy (KQ 2)
- Nonpharmacologic therapy versus inactive treatments, usual care, or no treatment (KQ 3)

Search protocols

Complete methods and data, including detailed search protocols and inclusion and exclusion criteria, for the five AHRQ reports summarized here have been published (Chou et al., April 2020; Chou et al., December 2020; Halker Singh et al., December 2020; McDonagh et al., April 2020; Skelly et al., April 2020). Briefly, study authors developed the search protocols using a standardized process with input from experts and the public. The review protocols were submitted for registration in the PROSPERO database prior to conducting the reviews. For each review, research librarians conducted searches on multiple electronic databases. For all reviews, searches were conducted on MEDLINE, Cochrane CENTRAL, and the Cochrane Database of Systematic Reviews; other databases that were utilized for one or more reviews (depending on the topic) were Embase PsycINFO, CINAHL, Scopus, and others. The searches were supplemented by a review of reference lists (including prior AHRQ and CDC reviews on these topics) (Chou et al., September 2014; Dowell et al., 2016; Skelly et al., 2018) and gray literature sources. Searches were conducted in August or September 2019 for the chronic pain reviews and in July or August 2020 for the acute pain reviews.

Summarizing the evidence

The reviews categorized magnitude of effects for pain and function using the same system as prior AHRQ reviews (Chou et al., 2017; Skelly et al., 2018). A small effect was defined for pain as a mean between-group difference following treatment of 0.5 to 1.0 points on a 0- to 10-point numeric rating scale (NRS) or visual analog scale (VAS) and for function as a standardized mean difference (SMD) of 0.2 to 0.5 or a mean difference of 5 to 10 points on the 0 to 100-point Oswestry Disability Index (ODI) (Fairbank & Pynsent, 2000), 1 to 2 points on the 0 to 24-point Roland-Morris Disability Questionnaire (RDQ) (Roland & Morris, 1983), or equivalent. A moderate effect was defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS (1 to 2 points on a 0- to 10-point NRS) and for function as an SMD of 0.5 to 0.8, or a mean difference of 10 to 20 points on the ODI, 2 to 5 points on the RDQ, or equivalent (Chou et al., 2017; Skelly et al., 2018). Large/substantial effects were defined as greater than moderate. We applied similar thresholds to other outcomes measured. Small effects using this system may not meet proposed thresholds for clinically meaningful effects (Ostelo et al., 2008). However, there is variability in estimated minimum clinically important differences across studies, and the clinical relevance of effects classified as small might vary for individual patients depending on preferences, baseline symptom severity, harms, cost, and other factors (Jayadevappa, Cook, & Chhatre, 2017; Keurentjes, Van Tol, Fiocco, Schoones, & Nelissen, 2012). The reviews also evaluated results based on dichotomous outcomes (e.g., likelihood of experiencing clinically meaningful improvement in pain or function, often defined as >30% or >50% improvement from baseline).

Evaluating quality of the evidence: the AHRQ method

The reviews used the AHRQ approach to synthesize and grade the strength of evidence (Berkman et al., 2015). The AHRQ approach is based on a systematic review of the evidence and provides an overall strength of evidence indicating the level of certainty (high, moderate, low, or

insufficient), based on similar factors considered in the CDC Advisory Committee on Immunization Practices (ACIP) adapted (Ahmed, Temte, Campos-Outcalt, & Schünemann, 2011; G. Lee & Carr, 2018) GRADE (Guyatt et al., 2008) approach (study limitations/risk of bias, consistency, directness, precision, reporting bias, and other factors [large strength of association, dose response, and plausible confounders strengthening observed findings]).

Evaluating the quality of the evidence: the ACIP-adapted GRADE method

Predicated on a systematic review of scientific evidence, the GRADE approach provides a transparent framework for grading the quality of evidence and strength of recommendations based on the evidence. GRADE has been adapted by the ACIP, (Ahmed et al., 2011; G. Lee & Carr, 2018) and CDC used the ACIP adaptation of the GRADE framework in this clinical practice guideline. Applying the ACIP GRADE framework, each body of evidence is initially categorized using a hierarchy that reflects the degree of confidence in the effect of a clinical action on health outcomes. The categories in the hierarchy (Box 2) are: 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), and type 4 evidence (clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations). The evidence is downgraded if issues are identified with regard to risk of bias, inconsistency, indirectness, imprecision, or publication bias; observational studies may be upgraded in certain situations (large strength of association, presence of dose response, or plausible effects of confounding would strengthen findings). That is, if it is likely that confounding would provide results opposite to the observed findings, it strengthens the confidence that the observed association is present. Based on these considerations, a final evidence type is assigned. Type 1 evidence indicates high confidence that the true effect is close to the estimate of the effect; type 2 evidence means that the

true effect is likely to be close to the estimate of the effect, but there is some uncertainty; type 3 evidence means that confidence in the effect estimate is limited (moderate uncertainty), and the true effect could differ substantially from the estimate of the effect; and type 4 evidence indicates that one has very little confidence in the effect estimate (high uncertainty), and the likelihood that the true effect differs from the estimate of the effect is high (Ahmed et al., 2011; Balshem et al., 2011). When no studies are available or the evidence is too limited to estimate effects, evidence is considered insufficient.

Evaluating the quality of the evidence: converting the AHRQ quality rating to the ACIP-adapted GRADE rating

The AHRQ approach uses a different method and terminology (high, moderate, low, or insufficient) to grade the strength of evidence (SOE) than the ACIP-adapted GRADE approach (evidence types 1, 2, 3, or 4) (Berkman et al., 2015). However, the underlying principles are similar, enabling translation from the AHRQ to CDC grades. A methodologist translated the AHRQ strength of evidence grades to CDC evidence types based on the information provided in the summary of evidence tables in the AHRQ reviews. Tables with GRADE clinical evidence review ratings of the evidence for the key clinical questions are available (http://stacks.cdc.gov/XXXXX *link TBD*). Evidence was categorized into the following types: type 1 (randomized clinical trials or overwhelming evidence from observational studies; generally equivalent to AHRQ high strength of evidence), type 2 (randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies; generally equivalent to AHRQ moderate strength of evidence), type 3 (observational studies, or randomized clinical trials with notable limitations; generally equivalent to most AHRQ low strength of evidence ratings), or type 4 (clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations; equivalent to AHRQ low strength of evidence with serious limitations). When no studies were available or the evidence was too limited to estimate effects,

evidence was assessed as insufficient. Results from meta-analyses conducted for the AHRQ reviews were reported when available; otherwise, the evidence was synthesized qualitatively.

Methods to develop the recommendations

CDC developed this clinical practice guideline using the approach developed by the GRADE working group (https://www.gradeworkinggroup.org/). Recommendations are based on the reviewed evidence. In the ACIP adapted GRADE framework, recommendations are assigned one of two categories (category A or B). Four major factors determine the category of the recommendation: the quality of evidence, the balance between desirable and undesirable effects, values and preferences, and resource allocation (e.g., costs to patients or health systems) (Andrews et al., 2013). Other considerations include feasibility and acceptability, and impact on equity (Welch et al., 2017). Recommendations are more likely to be category A when the evidence is higher quality, there is a greater balance of desirable relative to undesirable effects, resources and costs are lower, and when recommendations are less sensitive to differences in values and preferences. Category A recommendations generally apply to all persons in the group addressed in the recommendation and indicate a course of action that can be followed in most circumstances. Category B recommendations indicate that the recommendation may not apply to all persons in the group addressed in the recommendation; therefore, different choices will be appropriate for different patients and decisions should be individualized based on the individual patient's circumstances. For category B recommendations, clinicians must help patients arrive at a decision consistent with patient values and preferences, and specific clinical situations (shared decision-making) (Ahmed, 2013). In the GRADE approach, a particular quality of evidence does not necessarily result in a particular strength of recommendation (Andrews et al., 2013; Balshem et al., 2011; Guyatt et al., 2008). Although it is desirable for category A recommendations to be based on type 1 or type 2 evidence, category A recommendations can be made based on type 3 or type 4 evidence when the advantages of a clinical action are assessed as clearly outweighing the disadvantages based on a

consideration of benefits and harms, values and preferences, and costs, despite uncertainty in effect estimates (Andrews et al., 2013). The GRADE Working Group has presented several "paradigmatic" situations in which strong (category A) recommendations may be justified despite low quality evidence, for example, when high quality evidence suggests equivalence of two alternatives and low quality evidence suggests harm in one alternative, or when high quality evidence suggests modest benefits and low/very low quality evidence suggests possibility of catastrophic harm (Andrews et al., 2013). Category B recommendations are made when the advantages and disadvantages of a clinical action are more balanced or when there is more uncertainty with regard to whether benefits clearly outweigh harms.

In accordance with the ACIP adapted GRADE process, CDC drafted recommendations based on the clinical and contextual evidence (including benefits and harms, values and preferences, resource allocation). Draft recommendations focused on determining whether or not to initiate opioids for pain; opioid selection and dosage; opioid duration and follow-up; and assessing risk and addressing potential harms of opioid use. To help assure the draft guideline's integrity and credibility, CDC then began a multistep review process described in detail below.

Federal Advisory Committee review and recommendation

CDC sought recommendations on the draft updated clinical practice guideline from one of its federal advisory committees, the Board of Scientific Counselors of the National Center for Injury Prevention and Control (BSC/NCIPC). The BSC/NCIPC advises the Secretary of the Department of Health and Human Services (HHS), the Director of CDC, and the Director of NCIPC, and makes recommendations regarding scientific, programmatic, and research policies, strategies, objectives, projects, and priorities. The BSC/NCIPC also reviews progress toward injury and violence prevention. BSC/NCIPC members are special government employees appointed by the Secretary, HHS, or their designee, as CDC advisory committee members. Members are required to complete the Office of Government Ethics Form 450

annually to disclose relevant interests and report on their disclosures during meetings. Disclosures for the BSC/NCIPC are reported in this clinical practice guideline.

On December 4-5, 2019, CDC held a public meeting of the BSC/NCIPC (announced via *Federal Register* 84 FR 57021; 84 FR 65159) and provided a presentation on the background for updating the clinical practice guideline. CDC then requested the formation of an Opioid Workgroup (OWG), under the parent BSC, whose primary purpose would be to review a draft updated clinical practice guideline and to develop a report of their observations for the BSC/NCIPC (Centers for Disease Control and Prevention, 2021a). After considering CDC's presentations, the proposed OWG Terms of Reference, and public comments, the BSC/NCIPC voted unanimously to establish an OWG that reports to the BSC/NCIPC. CDC then held a public nomination process for prospective OWG members (Centers for Disease Control and Prevention, 2021a).

To provide background to the BSC/NCIPC for informing the creation of the OWG with a balance of perspectives, CDC identified audiences that would be: 1) directly affected by the clinical practice guideline, 2) directly involved with implementing or integrating recommendations into current practice, and 3) qualified to represent a specific discipline or expertise in alignment with the tasks of the workgroup for consideration by the BSC/NCIPC. Identified groups with perspectives that would support the workgroup's capacity included, but were not limited to, patients living with pain, family members and caregivers, clinicians, public health practitioners, and research scientists. CDC announced the call for nominations at the December 4-5, 2019, public meeting and heard recommendations from the public during the public comment opportunities, as well as from BSC/NCIPC members regarding recommendations for nominations. People interested in being considered for the workgroup were encouraged to submit self-nominations from December 4, 2019, through February 4, 2020. CDC's BSC/NCIPC received 255 nominations for the OWG.

After carefully reviewing clinical expertise, professional credentials, and diversity in perspectives of all nominees (including sex, race/ethnicity, geographic region, institutional affiliations, and personal experiences relevant to pain management and caring for patients with pain), the OWG's Designated Federal Officer (DFO) created a list of prospective workgroup members and sent invitations to participate along with conflict-of-interest disclosure forms. The OWG's DFO and the BSC/NCIPC's DFO reviewed conflict of interest disclosure forms. CDC's Strategic Business Initiatives Unit (SBIU), which oversees the Federal Advisory Committee Act program, also reviewed the OWG Terms of Reference, prospective OWG roster, curricula vitae, and conflict of interest disclosure forms and determined all reported financial or other conflicts of interest were not present or non-significant before finalizing selection. OWG members disclosed any potential topical conflicts of interest related to OWG meeting agenda items prior to each meeting. Disclosures of the OWG are reported in the clinical practice guideline.

The OWG had 23 members (Centers for Disease Control and Prevention, 2020d). In accordance with CDC guidance (Centers for Disease Control and Prevention, 2008, 2020c) that at least two BSC/NCIPC members must serve on the OWG, and one of the two members must serve as the workgroup chair, the OWG included a total of three BSC/NCIPC members, with one BSC/NCIPC member serving as the OWG chair. A NCIPC subject matter expert served as the OWG's DFO. OWG members included patients with pain, caregivers, and family members of patients with pain. The OWG also comprised clinicians and subject matter experts, with the following perspectives represented: primary care, pain medicine, public health, behavioral health, pharmacy, emergency medicine, medical toxicology, obstetrics/gynecology, bioethics, orthopedic surgery, plastic surgery, dentistry, sickle cell disease, substance use disorder treatment, and research. OWG members were diverse in regard to sex, race/ethnicity, geographic region, institutional affiliation, subject matter expertise, and personal

experiences. The CDC NCIPC OWG DFO presented the OWG roster and reviewed the Terms of Reference at the publicly held BSC/NCIPC meeting on July 22, 2020 (*Federal Register* 85 FR 30709; 85 FR 40290).

The OWG had a total of 11 meetings from October 2020 through June 2021. Before receiving the draft updated clinical practice guideline, the OWG held meetings to review and discuss the 2016 CDC Guideline, CDC's community engagement activities with patients, caregivers, and clinicians, and GRADE methodology. CDC NCIPC staff provided the OWG with the evidence reviews, public comments from BSC/NCIPC meetings, and summaries of community engagements for review before providing the OWG with the draft updated clinical practice guideline in March 2021. The OWG held 7 meetings to review and discuss the draft clinical practice guideline and develop a report summarizing their expert observations and findings for the BSC/NCIPC. The OWG report (BSC/NCIPC Opioid Workgroup Members, 2021) provided overall observations on overarching themes and draft clinical practice guideline recommendations. In addition, many members of the OWG developed a document entitled *OWG Guiding Principles* that was included as an appendix in the OWG report; this document outlines the "general process and principles by which the OWG approached their assigned tasks." These *Guiding Principles* included: minimize bias, scientific integrity, enhance inclusivity, patient and clinician centered, and historical context.

The OWG chair presented the OWG report at a public BSC/NCIPC meeting held on July 16, 2021 (*Federal Register* 86 FR 30048*)*. After hearing additional CDC presentations on the process and progress of the draft clinical practice guideline, discussion of the OWG report, and a two-hour public comment period, the BSC/NCIPC voted unanimously that CDC adopt the OWG report, while considering ideas and suggestions raised by the BSC/NCIPC and public during the meeting, and that the OWG's work be considered complete and the OWG sunsetted. After the meeting, the BSC/NCIPC provided their recommendations to HHS and CDC. CDC carefully considered the OWG's observations, BSC/NCIPC recommendations, and public comments when revising the draft updated clinical practice guideline.

781 **Federal partner engagement**

782 The BSC/NCIPC invited federal partners to serve as ex-officio members of the OWG, which
783 comprised representatives from the National Institute on Drug Abuse (NIDA) at the National Institutes of
784 Health (NIH), the Substance Abuse and Mental Health Services Administration (SAMHSA), FDA, and the
785 Indian Health Service (IHS). The BSC/NCIPC comprised ex-officio members from the Administration for
786 Children and Families, the Administration on Aging in the Administration for Community Living, the
787 National Institute for Occupational Safety and Health and the National Center for Health Statistics at the
788 CDC, the Health Resources and Services Administration, IHS, SAMHSA, and the National Institute on
789 Aging, the National Institute of Child Health and Human Development, NIDA, and the National Institute
790 of Mental Health at the NIH. Additional federal partners were engaged throughout the clinical practice
791 guideline update process. Federal partners reviewed the full draft clinical practice guideline as part of
792 CDC's agency clearance process.

793 **Public comment and community engagement**

794 CDC garnered input through *Federal Register* notices to better understand community
795 members' lived experiences and perspectives related to pain and pain management options before
796 drafting the updated clinical practice guideline. Through the *Federal Register* notice (85 FR 21441)
797 posted from April 17, 2020, through June 16, 2020, CDC invited input specifically on topics focused on
798 using or prescribing opioid pain medications, nonopioid medications, or nonpharmacological treatments
799 and received 5,392 public comments. Public comments were synthesized into common themes, utilizing
800 a CDC-funded analysis contract.

801 In addition, the Lab at the US Office of Personnel Management (OPM) worked with CDC to
802 design and implement community engagement opportunities to gain additional insight into the values
803 and preferences of patients, caregivers, and clinicians. For these opportunities, key groups included
804 patients with acute or chronic pain, patients' family members and/or caregivers, and clinicians who care

for patients with pain or conditions that can complicate pain management (e.g., opioid use disorder or overdose).

CDC planned to have individual conversations with patients, caregivers, and clinicians in person but pivoted to holding conversations with individuals in a virtual format due to the COVID-19 pandemic. CDC posted a companion *Federal Register* notice (85 FR 44303) from July 22, 2020, through August 21, 2020, to solicit input from patients, caregivers, and clinicians interested in participating in individual conversations. After the *Federal Register* notice closed, CDC and OPM randomly selected participants within each group (i.e., patients, caregivers, clinicians) from a total of 973 respondents. They also developed a randomly-selected waitlist of participants that they used to fill conversation appointments that were missed or cancelled by participants. The community engagement was authorized under the Generic Clearance for the Collection of Qualitative Feedback on Agency Service Delivery (OMB Control Number: 0920-1050) approval for the Paperwork Reduction Act. CDC and OPM conducted telephone and video conversations throughout September 2020 and spoke with 106 individuals, which included 42 patients, 21 caregivers, and 43 clinicians. Participating individuals lived and worked all over the United States and had diverse experiences with opioids. Participants provided verbal consent for their conversations to be recorded. A transcription service reviewed the conversation recordings to develop anonymized transcripts. CDC and OPM reviewed the anonymized transcripts to develop thematic summaries.

CDC and OPM also held two human-centered co-design workshops with staff from CDC and Centers for Medicare and Medicaid Services (CMS). Workshop topics included framing priority needs for public input, objectives for individual conversations, and synthesizing engagement strategies based on insights from public comments and conversations with patients, caregivers, and clinicians. Workshop participants included patients, caregivers, clinicians, clinical practice guideline authors, and other subject matter experts.

CDC also garnered input through oral and written public comment opportunities at and in conjunction with public BSC/NCIPC meetings. These public comment opportunities were announced through Federal Register notices (*Federal Register* 84 FR 57021; 84 FR 65159; 85 FR 30709; 85 FR 40290; 86 FR 1502; 86 FR 30048) and partner newsletters.

CDC reviewed thematic summaries of public comments, individual conversations, and the workshops to learn more about the values and preferences of patients, caregivers, clinicians, and experts before drafting the updated clinical practice guideline. After incorporating observations and comments on the draft clinical practice guideline from the BSC/NCIPC and agency clearance process, CDC will post the revised full draft clinical practice guideline in the Federal Register for public comment. The public comment period is anticipated to be open for 60 days. CDC will review and carefully consider all comments when revising the updated clinical practice guideline.

Peer review

This clinical practice guideline provides influential scientific information that could have a clear and substantial impact on public- and private-sector decisions. Therefore, peer review of the draft clinical practice guideline is required per the final information quality bulletin for peer review (https://www.whitehouse.gov/wp-content/uploads/2019/04/M-19-15.pdf).

Note: *at the time of developing this revision of the draft updated clinical practice guideline, the peer review process is ongoing. This information will be updated once peer review is complete.*

CDC selected peer reviewers based on scientific and subject-matter expertise, racial/ethnic diversity, diversity of experiences and perspectives, independence from the clinical practice guideline development process, and consideration of conflicts of interest. Specific effort was made to identify subject matter experts with knowledge and experience in topics such as chronic and acute pain management; clinical practice; health equity; mental health and well-being; opioids and opioid therapies; opioid tapering; opioid use disorder treatment; pharmacological and non-pharmacological

pain management; and surgical pain management. CDC assessed potential conflicts of interest with the same conflict of interest disclosure form used for selection of BSC/NCIPC OWG members. Conflict of interest forms will be reviewed by the NCIPC Associate Director for Science and confirmed by SBIU before finalizing selection. Any disclosures of the peer reviewers will be reported in the final published clinical practice guideline. After the peer reviewers have completed their reviews, CDC will post the names of peer reviewers on the CDC and the NCIPC Peer Review Agenda websites that are used to provide information about the peer review of influential government scientific documents. Peer reviewers will independently review the draft clinical practice guideline to determine the reasonableness and strength of recommendations; the clarity with which scientific uncertainties were clearly identified; and the rationale, importance, clarity, and ease of implementation of the recommendations. CDC will review and carefully consider peer review comments when revising the draft clinical practice guideline.

Summary of findings for clinical questions

Opioids for chronic pain

The AHRQ systematic clinical evidence review on opioids for chronic pain (Chou et al., April 2020) updated the 2014 AHRQ report (Chou et al., September 2014) and 2016 CDC update (Dowell et al., 2016) and expanded upon the prior reviews by adding evidence from randomized trials reporting short-term outcomes, including tramadol as an opioid intervention, addressing risks of co-prescribing benzodiazepines or gabapentin, and addressing effects of co-use of cannabis.

Effectiveness (benefits and harms)

For short-term (1 to <6 month) outcomes, based on over 70 placebo-controlled trials (evidence type 1), opioids were associated with beneficial effects versus placebo, but mean differences were

small: for pain, <1 point on a 0 to 10 scale and for function, a SMD of 0.22 (or <1 point on the 0 to 10 Brief Pain Inventory [BPI]) (Cleeland & Ryan, 1994) interference scale and <1 point on the 0 to 24 Roland-Morris Disability Questionnaire [RDQ]). Opioids were associated with a number of patients needed to treat (NNT) of approximately 6.7 to achieve one additional case of short-term pain relief (e.g., ≥30% improvement in pain). Analyses based on a combination of head-to-head (within study) comparisons as well as a meta-regression of placebo-controlled trials indicated an association between higher opioid dose and greater short-term effects on pain which appeared to plateau at around 50 mg morphine equivalent dose (MME)/day (evidence type 2). Evidence also indicated that effects of opioids dissipate with longer duration of therapy. Opioids were associated with a small mean improvement in short-term sleep quality (evidence type 2) versus placebo and a small mean short-term improvement in Short-Form 36-item (SF-36) (Ware & Sherbourne, 1992) mental health status (evidence type 1). Effects of opioids on short-term outcomes were generally consistent across opioid types (opioid agonist, partial agonist, or mixed medication agent). Effects on pain were somewhat greater for neuropathic than musculoskeletal pain (effects on pain about 0.5 point greater for neuropathic versus musculoskeletal pain on a 0 to 10 scale). Use of a crossover or enriched enrollment randomized withdrawal (EERW) design (a type of trial in which potential participants receive the study drug for a period of time in a prerandomization phase, and only those who benefit from the drug and can tolerate the side effects continue in the trial, randomly assigned to continue on the study drug or placebo [Furlan, Chaparro, Irvin, & Mailis-Gagnon, 2011]) was associated with greater effects on pain than parallel group or non-EERW studies.

Opioids were associated with increased risk versus placebo of discontinuation due to adverse events (number of patients treated to cause one adverse event [number needed to harm, NNH 10], and increased risk of gastrointestinal events [NNH 7.1 for nausea, 14.3 for vomiting, and 7.1 for constipation], somnolence [NNH 11.1], dizziness [NNH 12.5], and pruritus [NNH 14.3]) (evidence type 1).

There were few serious adverse events and no difference between opioids versus placebo in risk in the short-term trials (evidence type 2), but serious adverse events were not well-defined by the trials, the trials excluded higher risk patients (e.g., those with history of substance use disorder), and the trials were not designed to assess serious but less common harms such as overdose, opioid use disorder mortality, cardiovascular events, and fractures. EERW studies tended to report lower risk with opioids of discontinuation due to adverse events and gastrointestinal adverse events than non-EERW studies. Uncontrolled studies (studies without a non-opioid control group) were not included in the AHRQ review, though a recent systematic review with such studies found that rates of misuse ranged from 21 to 29% (range, 95% confidence interval [CI], 13 to 38%) and rates of addiction ranged from 8 to 12%(range, 95% CI, 3 to 17%), based on higher quality observational evidence (Vowles et al., 2015).

As in the 2014 AHRQ report and 2016 CDC update, the clinical evidence review identified no long-term (>1 year) randomized controlled trials (RCTs) of opioid therapy versus placebo. One new cohort study found long-term opioid therapy was not associated with improved pain, function or other outcomes versus no opioids (Veiga et al., 2019). New observational studies included in the new AHRQ review were consistent with the 2014 AHRQ report in finding an association between use of prescription opioids and risk of addiction, overdose, fractures, falls, and cardiovascular events (evidence type 3); a new study also found an association between opioid use and risk of all-cause mortality (Ray, Chung, Murray, Hall, & Stein, 2016) (evidence type 4). New observational studies were also consistent with the 2014 AHRQ report in finding associations between higher doses of opioids and risks of overdose, addiction, and endocrinological adverse events; new studies also found an association between higher dose and increased risk of incident or refractory depression (Scherrer, Salas, Copeland, et al., 2016; Scherrer, Salas, Sullivan, et al., 2016). Observational studies also indicated an association between co-prescription of gabapentinoids (Gomes et al., 2018; Gomes et al., 2017; Peckham, Fairman, & Sclar, 2018) or benzodiazepines (Dunn et al., 2010; Hernandez, He, Brooks, & Zhang, 2018; E. C. Sun et al.,

2017) and increased risk of overdose, with most pronounced risk occurring soon after initiation of these medications (evidence type 3). All observational studies were susceptible to residual confounding.

There were no differences across 16 trials between opioids versus nonopioids (most commonly, NSAIDs, gabapentinoids, and nortriptyline) in short-term pain, function, health status/quality of life, sleep quality, or mental health outcomes (evidence type 1 for function and 2 for other outcomes), though opioids were associated with increased risk of short-term adverse effects (evidence type 1 or 2). Most trials were <6 months; one trial of patients with chronic low back pain or pain associated with osteoarthritis (mean pain intensity 5.4 on a 0 to 10 scale at baseline) evaluated outcomes at 1 year (E. E. Krebs et al., 2018). It found no differences between stepped therapy with opioids versus stepped therapy starting with nonopioids in function, sleep, or mental health outcomes; opioids were associated with slightly worse effects (by ~0.5 point on a 0 to 10 scale) on pain (evidence type 2). Although tramadol was an option in step 3 of the nonopioid stepped therapy arm, only 11% received tramadol; mean opioid doses for stepped opioid therapy and stepped therapy starting with nonopioids were 26 vs. 1 MME/day, respectively, at 12 months.

There were also no differences between combination therapy versus a nonopioid alone in short-term effectiveness but increased risk of short-term adverse effects for combination therapy, based on six trials (evidence type 3). Combination therapy was associated with a small (5 to 13 MME/day) opioid-sparing effect versus opioid therapy alone, with little effect on pain. All trials of combination therapy evaluated patients with neuropathic pain and primarily evaluated gabapentinoids or nortriptyline. Evidence on long-term effects of combination therapy versus an opioid or nonopioid alone was lacking.

Opioid dosing strategies

Evidence on the effectiveness of different opioid dosing strategies remains very limited. One trial included in the 2014 AHRQ report found no differences between a more liberal dose escalation

strategy versus maintenance of current doses in pain, function, or discontinuation due to opioid misuse, but the difference in opioid doses between arms was small (52 vs. 40 mg MMD/day) (Naliboff et al., 2011) (evidence type 3). There were no clear differences between short- versus long-acting opioids (evidence type 3) or between different long-acting opioids (evidence type 2) in pain or function, but in most trials, doses were titrated to achieve adequate pain control. Evidence on comparative risks of methadone versus other opioids and risk of overdose remains limited and inconsistent. Evidence on the benefits and harms of different methods for initiating and titrating opioids, scheduled and continuous versus as-needed dosing of opioids, use of opioid rotation, and methods for titrating or discontinuing patients off opioids remains insufficient. The 2014 AHRQ report found buccal or intranasal fentanyl more effective than placebo or oral opioids for treatment of exacerbations of chronic pain, based on immediate effects (up to 2 hours after administration). None of the trials of buccal or intranasal fentanyl were designed to assess longer-term benefits or harms, and no new trials were identified for the 2020 systematic review. In 2007, the U.S. FDA released a public health advisory due to case reports of deaths and other life-threatening adverse effects in patients prescribed buccal fentanyl (U.S. Food and Drug Administration, 2007).

Risk mitigation strategies

New evidence on the accuracy of risk prediction instruments was consistent with the 2014 AHRQ report, which found highly inconsistent estimates of diagnostic accuracy, methodological limitations and few studies of risk assessment instruments other than the Opioid Risk Tool (L. R. Webster & Webster, 2005) and Screening and Opioid Assessment for Patients with Pain-Revised instrument (Butler, Fernandez, Benoit, Budman, & Jamison, 2008) (evidence type 3). Evidence on the effectiveness of risk mitigation strategies also remains very limited. One new observational study found provision of naloxone to patients prescribed opioids in primary care clinics was associated with decreased likelihood of emergency department visits, but no difference in overdose risk (evidence type 3) (Coffin et al.,

2016). Evidence on opioid tapering was largely limited to a trial that found a taper support intervention associated with better functional outcomes and a trend towards lower opioid doses versus usual opioid care (Sullivan et al., 2017) (evidence type 2). A cohort study found discontinuation of opioid therapy was associated with increased risk of overdose mortality versus continuation, but there was no statistically significant difference in risk of all-cause mortality (James et al., 2019). Findings should be interpreted with caution, because of potential confounding related to the reason for discontinuation.

No trial compared different rates of opioid tapering, though one observational study found an association between longer time to opioid discontinuation in patients on long-term, high-dose opioid therapy and decreased risk of opioid-related emergency department visit or hospitalization (Mark & Parish, 2019) (evidence type 3). The review did not identify any study that evaluated the effectiveness of risk mitigation strategies, such as use of risk assessment instruments, opioid management plans, patient education, urine drug screening, PDMP data review, monitoring instruments in patients prescribed opioids, more frequent monitoring intervals, pill counts, abuse-deterrent formulations, or avoidance of co-prescribing of benzodiazepines on risk of overdose, addiction, abuse or misuse.

Evidence on the effectiveness of interventions for opioid use disorder in patients with prescription opioid dependence or opioid use disorder was highly limited due to methodological shortcomings (small sample sizes, high attrition or crossover) and/or exclusion of patients with chronic pain.

Noninvasive nonpharmacologic treatment for chronic pain

The AHRQ systematic clinical evidence review (Skelly et al., April 2020) focused on commonly encountered pain conditions and frequently used interventions; selection of conditions for review was informed by stakeholder input.

Benefits

Chronic low back pain: The review found psychological therapies associated with small improvements versus usual care or an attention control for function and pain at short-, intermediate-, and long-term follow-up (evidence type 2). Exercise, low-level laser therapy, spinal manipulation, massage, yoga, acupuncture, and multidisciplinary rehabilitation were associated with improvements in function at short and/or intermediate term follow-up versus usual care, placebo, wait list, or inactive therapies; effects on pain were small for all therapies except yoga, for which benefits were moderate (evidence type 2 at short term for exercise, massage, and yoga; evidence type 3 for others). Massage, mindfulness-based stress reduction, acupuncture, and multidisciplinary rehabilitation were associated with small short-term improvement in pain versus control (evidence type 2); exercise, low-level laser therapy, and yoga were also associated with small to moderate short-term improvement in pain, though evidence was not as strong (evidence type 3). At intermediate term, spinal manipulation, yoga, multidisciplinary rehabilitation (evidence type 2) and exercise and mindfulness-based stress reduction (evidence type 3) were associated with improved pain versus sham, usual care, or attention control; effects were small for all therapies except for yoga, for which effects were moderate. Compared with exercise, multidisciplinary rehabilitation was associated with small improvements in function and pain at short and intermediate terms (evidence type 2).

Chronic neck pain: The AHRQ systematic clinical evidence review found low-level laser therapy (evidence type 2) and massage (evidence type 3) associated with improved short-term function and pain for chronic neck pain. The magnitude of effect was moderate for low-level laser therapy and small for massage. Exercise was associated with small improvement in long-term function versus attention control (evidence type 3) and combination exercise was associated with improved short- and long-term function and short-term pain versus wait list or attention control (evidence type 3). Acupuncture was associated with small improvements in short- and intermediate-term function versus sham, placebo, or usual care, but there were no differences in pain versus sham acupuncture, an intervention meant to

mimic acupuncture but without acupuncture effects (e.g., needles into non-acupuncture point, or non-penetrating needles/pressure on acupuncture points) (evidence type 3). Pilates was associated with improved short-term function (small effect) and pain (large effect) versus acetaminophen (evidence type 3).

Osteoarthritis pain: The AHRQ systematic clinical evidence review found that for knee osteoarthritis, exercise was associated with small improvements in short- and long-term function and pain versus usual care, no treatment, or sham (evidence type 2 for short-term and type 3 for long-term), and moderate improvement in intermediate-term pain and function (evidence type 3). For hip osteoarthritis, exercise was associated with small improvement in short-term function and pain versus usual care (evidence type 3). Functional improvement persisted at intermediate-term follow-up, but pain improvement did not (evidence type 3).

Fibromyalgia: The AHRQ systematic clinical evidence review found exercise, mind-body practices, and multidisciplinary rehabilitation, and acupuncture associated with small improvement in short-term function versus usual care or inactive treatments for fibromyalgia (evidence type 2 for acupuncture and evidence type 3 for others). At intermediate term, exercise, acupuncture, cognitive-behavioral therapy (CBT), mindfulness-based stress reduction, myofascial release, and multidisciplinary rehabilitation were associated with improvements in function versus inactive treatments, usual care, or waitlist (evidence type 2 for exercise and acupuncture and evidence type 3 for others). Effects on intermediate-term function were moderate for CBT and small for the other therapies. At long term, multidisciplinary rehabilitation was associated with persistent small improvement in function versus usual care, but not for pain (evidence type 3). Tai chi was associated with small improvement in function versus exercise at short- to intermediate-term follow-up (evidence type 3). Therapies associated with improved pain versus usual care, waitlist, no treatment, or inactive treatments were exercise (small effect, short and intermediate term; evidence type 2), CBT (small, short-term; evidence type 3),

mindfulness practices (small, intermediate-term; evidence type 3), and multidisciplinary rehabilitation (small, intermediate-term; evidence type 3).

Chronic tension headache: The AHRQ systematic clinical evidence review found spinal manipulation was associated with moderate improvement in short-term pain and small improvement in function versus usual care for chronic tension headache (evidence type 3). For other interventions, evidence was sparse, and the majority of trials had serious methodological limitations.

Harms

Across conditions, data on harms of nonpharmacological therapies was limited, but no evidence suggested serious harms. Although reporting on harms was suboptimal, among studies that reported data, non-serious treatment-related adverse events (e.g., discomfort, soreness, bruising, increased pain, and worsening of symptoms) were infrequently reported, there were few withdrawals from nonpharmacological therapies due to adverse events, and there were no differences between comparison groups (either usual care/no nonpharmacological therapy or another therapy) in the frequency of intervention-related adverse events or withdrawals (evidence type 2 or 3).

Nonopioid pharmacologic treatments for chronic pain

Benefits

For neuropathic pain, the AHRQ systematic clinical evidence review (McDonagh et al., April 2020) found anticonvulsants (gabapentin, pregabalin, and oxcarbazepine) were associated with small short-term improvement in pain versus placebo (evidence type 2), with no difference between pregabalin versus gabapentin enacarbil (evidence type 3). The antidepressant duloxetine was associated with small improvements in short-term pain, function, and quality of life versus placebo in patients with diabetic peripheral neuropathy (evidence type 2 for pain and quality of life and type 3 for function).

Tetrahydrocannabinol (THC) and cannabidiol (CBD) oral spray had inconsistent effects on pain in patients with multiple sclerosis or with allodynia (evidence type 3). Topical capsaicin was not associated with significant effects on pain versus placebo, or effects were below the threshold for a small effect (evidence type 2).

For fibromyalgia, the serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants milnacipran and duloxetine were associated with small, short- and intermediate-term improvements in pain and quality of life versus placebo; a small beneficial effect on function was only observed at short-term (evidence type 2). The anticonvulsants pregabalin and gabapentin were associated with small short-term improvements in pain and function versus placebo; there were no effects on quality of life (evidence type 2). Memantine was associated with moderate intermediate-term improvements in pain, function, and quality of life versus placebo (evidence type 3).

For osteoarthritis, NSAIDs were associated with small short-term improvement in pain (evidence type 2) and function (evidence type 1). Topical diclofenac was associated with small improvement in short-term pain (evidence type 2) and function (evidence type 3) versus placebo. Duloxetine was associated with small improvement in pain severity, function and quality of life; and moderate improvement in likelihood of a pain response (evidence type 1). Acetaminophen was not associated with improvement in pain or function versus placebo (evidence type 3).

For inflammatory arthritis, NSAIDs were associated with small improvements in short-term pain and function versus placebo (evidence type 2); effects on pain and function were small at intermediate-term follow-up (evidence type 3). At long-term follow-up effects on pain were large, with no effects on function (evidence type 3).

For low back pain, duloxetine was associated with a small short-term improvement in pain intensity and likelihood of a pain response versus placebo, but improvements in function and quality of life did not meet the threshold for small improvement (evidence type 2).

Harms

Across all classes of nonopioid therapies, the AHRQ systematic clinical evidence review found that the incidence of serious adverse events (SAE) was low; however, the trials were not designed to assess SAEs and there were few SAEs (evidence type 3).

Antidepressants were associated with increased risk of withdrawal due to adverse events (WAE) versus placebo. SNRI antidepressants were associated with moderate to large increases in risk of nausea and excessive sweating (evidence type 2 or 3). Duloxetine was associated with a large, dose-dependent, increase in sedation versus placebo (evidence type 2 or 3).

With regard to anticonvulsants, oxcarbazepine was associated with a large increase in risk of WAEs versus placebo (evidence type 2). Pregabalin and gabapentin were associated with moderate increased risk of WAEs (evidence type 2), with an association between higher doses of pregabalin and increased risk. Pregabalin and gabapentin were associated with large increases in blurred vision, dizziness, weight gain, and cognitive effects (e.g., confusion) (evidence type 2). Additionally, pregabalin was associated with large increases in risk of peripheral edema and sedation (evidence type 2).

NSAIDs were associated with increased risk of WAEs versus placebo; the magnitude was small for ibuprofen and diclofenac and moderate for naproxen (evidence type 2). The risk of any cardiovascular event was not significantly elevated for NSAIDs as a group, but diclofenac was associated with small increase in risk, particularly in the first 6 months, and with higher doses (evidence type 2). Versus placebo, the risk of major coronary events was elevated with diclofenac and celecoxib (moderate effect) and with ibuprofen (large effect). For every 3000 patients treated with diclofenac or celecoxib,

there were an estimated 3 additional major coronary events. There was no difference in cardiovascular events between celecoxib versus nonselective NSAIDs in the intermediate or long term (evidence type 2). The risk of serious upper gastrointestinal events was increased with diclofenac (moderate effect) and ibuprofen or naproxen (large increase), particularly in the first 6 months of treatment (evidence type 1 to 2). In the intermediate term, diclofenac and naproxen were associated with large increase in risk of hepatic harms (evidence type 1 to 2).

Acetaminophen was not associated with increased risk of short- or intermediate-term WAEs versus placebo (evidence type 3). Capsaicin was associated with large increase in risk of application site pain (evidence type 2) and a small increased risk of erythema (evidence type 3). Cannabis as oral dronabinol solution was associated with large increase in risk of dizziness, and as tetrahydrocannabinol/cannabidiol was associated with large increase in risk of WAEs, dizziness, and nausea (evidence type 3).

Treatments for acute pain

The AHRQ systematic clinical evidence review (Chou et al., December 2020) found that most trials of treatments for acute pain focused on effects on pain at short-term (up to 1 week) follow-up. Evidence was somewhat stronger for pharmacological than nonpharmacological therapies.

For acute surgical dental pain (evidence type 3) and kidney stone pain (evidence type 2), the AHRQ systematic clinical evidence review found that opioids were associated with small to moderate increases in pain or need for rescue medication use versus NSAIDs. Findings for postoperative pain were somewhat inconsistent. Although opioids were associated with increased likelihood of repeat or rescue medication use at 1 day to 1 week (evidence type 3), evidence on pain intensity was insufficient due to inconsistency. Results for postoperative pain were based on a small number of trials and pain related to a limited set of surgical procedures (most commonly cesarean section, anterior cruciate ligament (ACL)

reconstruction, knee arthroplasty, and cholecystectomy), limiting generalizability to other surgical procedures. Opioids were associated with increased risk of adverse events such as nausea, dizziness, and sedation versus nonopioid pharmacologic therapies (evidence type 2 or 3). The trials were not designed to assess SAEs, and few such events were reported. Evidence on opioids versus acetaminophen was somewhat mixed: for dental pain, the systematic clinical evidence review found opioids were associated with small improvement in pain outcomes on some measures (evidence type 2), but for kidney stone pain, opioids were associated with small increase in pain (evidence type 2). Evidence on NSAIDs versus acetaminophen was also somewhat mixed: for dental pain, evidence indicated that NSAIDs were associated with moderate to large decrease in pain (evidence type 2), but for kidney stone pain, evidence was insufficient. Evidence on nonopioid pharmacologic therapies other than NSAIDs or acetaminophen was very limited.

Evidence on nonpharmacological therapies for acute pain was limited. For low back pain, the AHRQ systematic clinical evidence review found heat therapy was associated with a moderate decrease in pain versus usual care or placebo at 1 day to <1 week and at 2 to <4 weeks (evidence type 2 to 3). There may be no difference between spinal manipulation versus inactive controls for non-radicular low back pain (evidence type 2 to 3), though one trial of patients with radiculopathy found manipulation was associated with increased likelihood of improvement in pain at 2 to <4 weeks, and at ≥4 weeks (evidence type 3) (Santilli, Beghi, & Finucci, 2006). Acupuncture was associated with moderate improvement in pain and function versus an NSAID for low back pain, but findings were based on one trial that evaluated one session of acupuncture and a single dose of an NSAID (evidence type 3) (Shin et al., 2013). For postoperative pain, there was type 3 evidence that massage might have some effectiveness, with likely no difference between cold therapy versus no cold therapy, with the possible exception of decreased pain medication use at <1 week. There was also limited evidence supporting effectiveness of acupressure for acute musculoskeletal pain (evidence type 3). Reporting of harms for

nonpharmacologic therapies was suboptimal. However, the noninvasive nonpharmacologic therapies evaluated in the AHRQ systematic clinical evidence review were generally not thought to be associated with serious harms, and harms were few when reported.

Trials of opioid therapy for acute pain were not designed to evaluate effects on long-term use of opioids or outcomes such as misuse or development of opioid use disorder. Limited evidence from observational studies found being prescribed an opioid for acute low back pain or after minor or elective surgical procedures was associated with increased likelihood of opioid use at longer term (e.g., 6 months or 1 year) follow-up (evidence type 3). Evidence on factors associated with opioid prescribing in patients with acute pain conditions was very limited, and suggested that legislation mandating use of prescription drug monitoring program data prior to prescribing was not associated with decreases in opioid prescribing for low back pain or postoperative pain. No studies were identified that evaluated the accuracy or effectiveness of risk assessment instruments to inform use of opioids for acute pain.

Treatments for acute episodic migraine

The AHRQ review on treatments for acute episodic migraine (Halker Singh et al., December 2020) found limited evidence on the benefits and harms of opioids. It found that opioids might be associated with decreased pain versus placebo, but worse pain outcomes versus nonopioid pharmacological therapy (evidence type 3). Most outcomes were assessed at short-term (2 hours or 1 day) follow-up. Opioids were associated with increased risk of adverse events, though evidence on serious adverse events was lacking. There were no studies on instruments for predicting opioid misuse, opioid use disorder, or overdose, or risk mitigation strategies in patients prescribed opioids for migraine.

The AHRQ review found stronger (type 1 or 2) evidence supporting the effectiveness of several established nonopioid pharmacological therapies for improving pain resolution in acute episodic migraine, including triptans, NSAIDs, dihydroergotamine, and ergotamine plus caffeine. Evidence also

favored antiemetics versus placebo or no antiemetic but was more limited (evidence type 3). Newer treatments (calcitonin gene-related peptide [CGRP] antagonists [gepants] and the 5-HT1F receptor antagonist lasmiditan) were associated with reduced pain and improved function versus placebo (evidence type 2 or 3). However, lasmiditan was associated with increased risk of severe adverse events (most commonly, dizziness; evidence type 3); evidence on serious adverse events of CGRP antagonists was insufficient.

Evidence on nonpharmacological therapy for acute episodic migraine was sparse. There was moderate evidence (evidence type 2) supporting remote electrical neuromodulation. More limited evidence (evidence type 3) supported acupuncture, chamomile oil, external trigeminal nerve stimulation, and eye movement desensitization reprocessing. There was insufficient evidence to determine risk of serious adverse events with nonpharmacological therapies for acute episodic migraine.

Contextual evidence reviews

Patient and clinician values and preferences

Opioids for chronic pain

A Contextual Evidence Review conducted for the 2016 CDC Guideline (Dowell et al., 2016) found data indicating that physicians frequently lacked confidence in their ability to safely prescribe opioids, predict or identify prescription medication misuse or opioid use disorder, or discuss these issues with their patients. Clinicians reported favorable beliefs and attitudes about effects of opioids on pain and quality of life; however, they also had concerns about risk of opioid use disorder and overdose, yet did not consistently utilize risk mitigation strategies (e.g., use of PDMP data, urine toxicology testing, and/or opioid treatment agreements). Evidence on patient values and preferences was limited but indicated

unfamiliarity with some terms ("opioids"), more familiarity with the term "narcotics" but an association between "narcotics" and "addiction" or "abuse," and concerns about addiction and abuse. Side effects such as nausea, constipation, and somnolence (rather than pain relief) accounted for most of the variation in patient preferences regarding use of opioids. Patients prescribed high dose opioids reported reliance on opioids, and ambivalence or uncertainty about benefits and side effects.

The AHRQ review identified some new information on preferences and values. A survey of 961 clinicians found that 82% were reluctant to prescribe opioids and less than half (47%) expressed confidence in caring for patients with chronic noncancer pain (Ebbert et al., 2018). Sixty-seven percent were aware of the 2016 CDC guideline and 55% were enrolled in the state PDMP; 2% always or frequently prescribed naloxone to patients on opioids, although results are difficult to interpret as the study did not specify whether patients met 2016 CDC Guideline criteria for naloxone. Guideline awareness was associated with increased confidence in caring for patients with chronic pain. Other surveys found negative attitudes or concerns regarding prescription opioid use disorder, but beliefs in potential effectiveness of opioids for treating pain and support for policies and guidelines aimed at mitigating risks, with increased confidence when following "best practices" (Kennedy-Hendricks et al., 2016; D. H. Lin et al., 2017; Razouki, Khokhar, Philpot, & Ebbert, 2019).

Regarding patient preferences and values, a new systematic review found that among various opioid-related outcomes (effects), patients ranked pain relief, nausea, and vomiting as most important, followed by constipation (Goshua et al., 2018). "Addiction" was only evaluated in two studies and rated as less important than pain relief. An online (non-peer reviewed) survey of over 3000 patients 1 year after the release of the 2016 CDC Guideline found that 84% reported more pain and worse quality of life and 42% said they had considered suicide; however, the survey did not attempt to sample patients with chronic pain using a rigorous methodological approach (Pain News Network, 2017).

Noninvasive nonpharmacological treatments for chronic pain

The Contextual Evidence Review found that evidence on patient values and preferences related to noninvasive nonpharmacological treatments for chronic pain was limited. A Gallup poll found that 78% of Americans preferred nonpharmacological therapies (e.g., physical therapy and chiropractic care) to address pain over prescribed pain medication (Rosenberg et al., 2008). Another survey indicated frequent use of complementary and integrative therapies for chronic pain (Francois, Lanier, Marich, Wallendorf, & Van Dillen, 2018).

Clinicians generally agreed with use of guideline-supported therapies and therapies supported by evidence, including nonpharmacological therapies; clinicians also felt that treatments should be credible and individualized to the patient (Cottrell, Foster, Porcheret, Rathod, & Roddy, 2017; Dima et al., 2013). Clinician concerns regarding nonpharmacological treatments included costs and safety (Cottrell et al., 2017). Surveys indicated high support for use of exercise therapy, complementary medicine therapies, and psychological therapies (Cottrell, Roddy, & Foster, 2010; Cowell et al., 2018; Driver, Kean, Oprescu, & Lovell, 2017); clinicians also supported chronic pain management informed by a biopsychosocial framework or using a multidimensional approach (Holden, Nicholls, Young, Hay, & Foster, 2009). Some barriers to use of therapies included lack of knowledge or expertise and uncertainty regarding potential benefits (Cottrell et al., 2010; Cowell et al., 2018; Dima et al., 2013; Heyward et al., 2018; Holden et al., 2009; Sierpina, Levine, Astin, & Tan, 2007).

Nonopioid pharmacological treatments for chronic pain

The Contextual Evidence Review found limited evidence on clinician and patient values and preferences related to nonopioid pharmacological treatments. Evidence described variability in patient preferences regarding nonopioid pharmacological treatments, interest in medical cannabis, cost as an important consideration, high priority on pain reduction as well as side effects and harms (including risk

of OUD), and high value for having alternatives to opioids (Mühlbacher et al., 2015; Patel et al., 2016; Turk et al., 2020). A survey of pharmacists in Canada found that 38% agreed that non-prescription analgesics should be first line for chronic low back pain and 79% agreed that tricyclic antidepressants are effective for peripheral diabetic neuropathy (R. C. Wielage, Bansal, Andrews, Klein, & Happich, 2013).

Treatments for acute pain

The Contextual Evidence Review found limited evidence suggesting variability in patient values and preferences regarding treatments for acute pain (Fullen et al., 2008; Hallway et al., 2019), with some evidence of high satisfaction when postoperative pain was managed using an opioid-sparing pathway (Swenson, Prashar, Mangino, Thode, & Singer, 2019). There was also variability in clinician values and preferences regarding acute pain treatments that were impacted by clinical specialty, knowledge regarding effectiveness, and costs; negative attitudes towards acute pain conditions were associated with less likelihood of using or re-dosing opioids (Cherkin, Deyo, Wheeler, & Ciol, 1995; Fullen et al., 2009; Glassberg et al., 2013; Green, Wheeler, & LaPorte, 2003; Mikhail, Korner-Bitensky, Rossignol, & Dumas, 2005). A systematic review found inconsistent evidence that education increased clinician adherence with acute low back pain guideline recommendations in terms of referral rates to physiotherapy (C. C. Lin et al., 2018).

Treatments for acute episodic migraine

The Contextual Evidence Review found very limited evidence on clinician and patient values and preferences related to treatments for acute episodic migraine. One survey found that patients with headaches (primarily episodic or chronic migraine) prioritized efficacy of treatment over the safety or route of administration and preferred oral over parenteral medications (Adelman & Belsey, 2003). A survey of Canadian pharmacists found that 42% agreed that migraine patients should try non-

prescription prior to prescription medications and 53% agreed that triptans should be reserved until failure of at least two other prescription medications (R. C. Wielage et al., 2013).

Costs and cost-effectiveness

Opioid therapy for chronic pain

The Contextual Evidence Review conducted for the 2016 CDC Guideline estimated (based on studies published after 2010) yearly direct and indirect costs related to prescription opioids at $53.4 billion for nonmedical use of prescription opioids; $55.7 billion for abuse, dependence (i.e., opioid use disorder), and misuse of prescription opioids; and $20.4 billion for opioid-related overdoses (Birnbaum et al., 2011; Hansen, Oster, Edelsberg, Woody, & Sullivan, 2011; Inocencio, Carroll, Read, & Holdford, 2013). In 2012, total expenses for outpatient prescription opioids were estimated at $9.0 billion, an increase of 120% from 2002 (Stagnitti, 2001). Based on a large national sample of 2008 claims data, direct costs of opioids in patients with osteoarthritis were estimated at $287.4 per patient, but there was wide variability in estimates (SD $1,652.1) (Gore, Tai, Sadosky, Leslie, & Stacey, 2012). One study estimated costs of urine toxicology testing (including screening and confirmatory tests) at $211 to $363 per test (Laffer et al., 2011).

The AHRQ report included data that estimated the total economic burden of fatal overdose, abuse, and dependence of prescription opioids in 2013 at $78.5 billion, with $28.9 billion related to increased healthcare and substance use disorder treatment costs (Florence, Zhou, Luo, & Xu, 2016). More recent data indicate that spending on opioid prescriptions peaked at $1.6 billion in 2009, with a decrease to $1.2 billion in 2016 (Cox, Rae, & Sawyer, 2018). However, costs of treatment for opioid use disorder and overdose increased ($646 million in 2009 and $2.6 billion in 2016). Data also indicate that Medicaid spending on opioids has declined since 2014, though spending on buprenorphine (a partial

opioid agonist often used to treat opioid use disorder) has increased (Young, 2019), likely because of greater numbers of individuals accessing medication and treatment for opioid use disorder (MOUD).

No study was identified that formally evaluated the cost-effectiveness of opioid therapy versus no opioid therapy or nonopioid pharmacological therapy for noncancer pain. A modeling study that estimated 80% of opioid overdose deaths to be attributable to illicit opioids projected that interventions targeting prescription opioid misuse such as prescription monitoring programs would decrease the number of opioid overdose deaths by 3.0% to 5.3% (Chen et al., 2019). There were also no cost-effectiveness analyses of risk mitigation strategies in persons prescribed opioids for chronic pain. A systematic review that included 43 economic evaluation studies of treatments for opioid use disorder found evidence supporting the cost-effectiveness of methadone therapy, with less evidence for other opioid use disorder therapies (Murphy & Polsky, 2016). Additional analyses from the UK and California also found treatment for opioid use disorder to be cost-effective or cost saving (Kenworthy et al., 2017; E. Krebs et al., 2018).

Noninvasive nonpharmacological treatments for chronic pain

The Contextual Evidence Review found that for nonpharmacological treatments covered by commercial insurers, out-of-pocket costs ranged from $25 to $60 per visit ($150 to $720 for a 6- to 12-visit course of therapy) (Heyward et al., 2018). Studies found that a number of nonpharmacologic therapies were cost-effective for various chronic pain conditions. For osteoarthritis, cost-effective interventions (relative to a comparison such as no therapy or usual care) included exercise, acupuncture, and transcutaneous electrical nerve stimulation (Center for Health Information and Analysis, 2015; Coupe et al., 2007; Dagenais, Caro, & Haldeman, 2008; Hurley et al., 2007; Jessep, Walsh, Ratcliffe, & Hurley, 2009; MacPherson et al., 2017; Oppong et al., 2015; Sevick et al., 2000; Sevick, Miller, Loeser, Williamson, & Messier, 2009). For low back pain, cost-effective interventions included interdisciplinary

rehabilitation, exercise, yoga, acupuncture, spinal manipulation, cognitive behavioral therapy, mindfulness based stress reduction, biofeedback, and multidisciplinary rehabilitation (Aboagye, Karlsson, Hagberg, & Jensen, 2015; Andronis et al., 2017; Driessen, Lin, & van Tulder, 2012; Haines & Bowles, 2017; Herman et al., 2017; Herman, Lavelle, Sorbero, Hurwitz, & Coulter, 2019; C. W. Lin, Haas, Maher, Machado, & van Tulder, 2011; Suni et al., 2018; Tsertsvadze et al., 2014). For neck pain, cost-effective interventions included manual therapy, physiotherapy, acupuncture, exercise, and spinal manipulative therapy (Essex et al., 2017; Herman et al., 2019; Miyamoto, Lin, Cabral, van Dongen, & van Tulder, 2019; R. L. Robinson & Jones, 2006; van der Velde et al., 2016; Willich et al., 2006). For fibromyalgia, cost-effectiveness analyses of nonpharmacological therapies was very limited (Luciano et al., 2014), but some evidence suggested that cognitive behavioral therapy dominated (associated with cost savings and greater benefits) pharmacological therapy or usual care (Hsiao & Fraenkel, 2019).

Nonopioid pharmacologic treatments for chronic pain

The Contextual Evidence Review found some evidence indicating that nonopioid pharmacological therapies are cost-effective for chronic pain. For osteoarthritis and low back pain, there was some evidence that nonopioid pharmacological therapies (NSAIDs, duloxetine) are cost-effective versus opioids (Huelin, Pokora, Foster, & Mould, 2012; Ivanova, Birnbaum, Kantor, Schiller, & Swindle, 2012; R. Wielage, Bansal, Wilson, Klein, & Happich, 2013); studies also found NSAIDs, duloxetine, and pregabalin cost-effective versus usual care or no treatment (Huelin et al., 2012; Ivanova, Birnbaum, Kantor, Schiller, & Swindle, 2014; Morera-Dominguez, Ceberio-Balda, Florez-Garcia, Masramon, & Lopez-Gomez, 2010; O'Connor, 2009). For neuropathic pain, cost-effective treatments included tricyclic antidepressants, duloxetine, pregabalin, and topical capsaicin or lidocaine (Armstrong, Malone, McCarberg, Panarites, & Pham, 2011; Beard et al., 2011; Cepeda & Farrar, 2006; Darba et al., 2014; de Salas-Cansado, Perez, Saldana, Navarro, & Rejas, 2012; J. Gordon et al., 2012; Kirson et al., 2010; Liedgens et al., 2008; Mankowski, Patel, Trueman, Bentley, & Poole, 2016; Parker, Huelin, Khankhel,

Wasiak, & Mould, 2015; Tarride, Gordon, Vera-Llonch, Dukes, & Rousseau, 2006; E. Q. Wu et al., 2006; N. Wu, Chen, Boulanger, Rao, & Zhao, 2011; Zhao et al., 2010). For fibromyalgia, cost-effective treatments included duloxetine, pregabalin, and amitriptyline, though analyses of relative cost-effectiveness among these therapies were inconsistent (Burke et al., 2012; Gan et al., 2004; Gore, Tai, Chandran, Zlateva, & Leslie, 2012; Harnett et al., 2011; Kleinman et al., 2011; Lloyd, Boomershine, Choy, Chandran, & Zlateva, 2012; P. Sun et al., 2014; Zhao, Sun, & Watson, 2011).

Treatments for acute pain

The Contextual Evidence Review found limited evidence exercise was cost-effective for acute low back pain and interdisciplinary rehabilitation cost-effective for low back pain that was identified as high risk for becoming chronic (Essex et al., 2017; Rogerson, Gatchel, & Bierner, 2010; Seferlis, Lindholm, & Nemeth, 2000). There was limited evidence that acetaminophen and spinal manipulation were not cost-effective for acute low back pain (the acetaminophen analysis was based on a randomized trial that found acetaminophen to be ineffective for acute low back pain and the spinal manipulation analysis was based on a cohort study that found that manipulation for acute low back pain did not reduce follow-up visits or days of sick leave for low back pain) (C. C. Lin et al., 2018; Walker, Mertens, Schmidt, & Chenot, 2017). One cohort study of patients with postsurgical pain found use of long-acting opioids within 30 days associated with greater costs of services ($11,900 vs. $8,400, p<0.0001) (Gold, Strassels, & Hansen, 2016).

Treatments for acute episodic migraine

The Contextual Evidence Review found that studies on costs and cost-effectiveness of treatments for acute episodic migraine focused almost exclusively on triptans. Triptans were consistently found to be associated with low costs per pain-free episode and other outcomes (e.g., migraine-disability days averted) (Asseburg et al., 2012; Belsey, 2004; Cady, Sheftell, Lipton, Kwong, &

O'Quinn, 2001; Kelman & Von Seggern, 2006; Lofland et al., 2001; Lofland & Nash, 2005; Mullins, Subedi, Healey, & Sanchez, 2007; Perfetto, Weis, Mullins, Subedi, & Healey, 2005; P. Williams & Reeder, 2004). Triptans were dominant (more effective and less costly) over fixed-dose combination of ergotamine tartrate plus caffeine (Zhang & Hay, 2005).

Recommendations

This clinical practice guideline includes 12 recommendations (Box 1) for clinicians who are prescribing opioids for outpatients aged ≥18 years with acute (duration <1 month) pain, subacute (duration of 1-3 months) pain, or chronic (duration of >3 months) pain outside of sickle cell disease-related pain management, cancer pain treatment, palliative care, and end-of-life care. Refer to the earlier section on scope and audience for further details on clinicians and patients and on definitions of acute, subacute, and chronic pain. In accordance with the ACIP adapted GRADE process, CDC based the recommendations on consideration of clinical evidence, contextual evidence (including benefits and harms, values and preferences, resource allocation), and expert opinion. Expert input is reflected within the recommendation rationales. For each recommendation statement, CDC notes the recommendation category (A or B) and the type of the evidence (1, 2, 3, or 4) supporting the statement (Box 2).

Category A recommendations indicate that most patients should receive the recommended course of action; category B recommendations indicate that different choices will be appropriate for different patients, requiring clinicians to help patients arrive at a decision consistent with patient values and preferences and specific clinical situations. Consistent with the ACIP (Ahmed, 2013; Centers for Disease Control and Prevention, 2018a) and GRADE process (Balshem et al., 2011), category A recommendations were made, even with type 3 and 4 evidence, when there was broad agreement that the advantages of a clinical action greatly outweighed the disadvantages based on a consideration of benefits and harms, values and preferences, and resource allocation. Category B recommendations

were made when there was broad agreement that the advantages and disadvantages of a clinical action were more balanced, but advantages were significant enough to warrant a recommendation. Recommendations were associated with a range of evidence types, from type 1 to type 4.

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

- A number of nonpharmacological treatments and a number of nonopioid medications are associated with improvements in pain and/or function that are reportedly comparable to improvements associated with opioid use.
- There is evidence that several noninvasive, nonpharmacologic interventions improve chronic pain and function, with small to moderate effects in specific pain conditions, and are not associated with serious harms. Compared with medication treatment, for which benefits are anticipated while patients are taking the medication but are not usually expected to persist following completion of treatment (once patients stop taking the medication), several noninvasive, nonpharmacologic interventions are associated with improvements in pain and/or function that are sustained following treatment.
- Nonopioid drugs, including SNRI antidepressants, pregabalin/gabapentin, and NSAIDs, are associated with small to moderate improvements in chronic pain and function. Drug class-specific adverse events include serious cardiovascular, gastrointestinal, or renal effects with NSAIDs and sedation with anticonvulsants.
- Opioid therapy is associated with similar or decreased effectiveness for pain and function versus NSAIDs across several acute pain conditions, with small improvements in short-term (1 to <6 months) pain and function compared with placebo, with increased short-term harms compared with placebo, and with evidence of attenuated pain reduction over time (between 3 and 6 months versus between 1 and 3 months). There is evidence from observational studies of an association between opioid use for acute pain and long-term opioid use. Evidence on long-term

effectiveness of opioids remains very limited; a long-term (12 months) randomized trial of stepped therapy for chronic musculoskeletal pain found no difference in function and higher pain intensity after starting with opioid therapy compared to starting with nonopioid therapy. There is evidence of increased risk of serious harms (including opioid use disorder and overdose) with long-term opioid therapy that appears to increase with increase in opioid dosage, without a clear threshold below which there is no risk. There is no validated, reliable way to predict which patients will suffer serious harm from opioid therapy and no reliable way to predict which patients will benefit from opioid therapy.

- It can be very challenging for clinicians and patients to discontinue opioids after extended periods of continuous opioid use. Tapering or discontinuing opioids in patients who have taken them long-term can be associated with significant risks (U.S. Food and Drug Administration, 2019c), particularly if opioids are tapered rapidly or patients do not receive effective support.
- Patients, caregivers, and clinicians responded to CDC with invited input regarding their lived experiences and perspectives related to pain and pain management options. Key themes expressed included strained patient-provider relationships and the need for patients and providers to make shared decisions, the impact of misapplication of the 2016 CDC Guideline, inconsistent access to effective pain management solutions, and achieving reduced prescription opioid use through diverse approaches.

Each of the 12 recommendations is followed by a rationale for the recommendation, with considerations for implementation noted immediately below the recommendation statement. These bulleted implementation considerations offer practical insights meant to further inform clinician-patient decision-making for the respective recommendation and are not meant to be rigidly or inflexibly followed. The recommendations are grouped into four areas for consideration:

- Determining whether or not to initiate opioids for pain

- Opioid selection and dosage
- Opioid duration and follow-up
- Assessing risk and addressing potential harms of opioid use

In addition, these five guiding principles should broadly inform implementation across recommendations:

1. Acute, subacute, and chronic pain need to be appropriately and effectively treated independent of whether opioids are part of a treatment regimen.

2. Recommendations are voluntary and are intended to support, not supplant, individualized, person-centered care. Flexibility to meet the care needs and the clinical circumstances of a specific patient are paramount.

3. A multimodal and multidisciplinary approach to pain management attending to the physical health, behavioral health, long-term services and supports, and expected health outcomes and well-being of each person is critical.

4. Special attention should be given to avoid misapplying this updated clinical practice guideline beyond its intended use or implementing policies purportedly derived from it that might lead to unintended consequences for patients.

5. Clinicians, practices, health systems, and payers should vigilantly attend to health inequities, provide culturally and linguistically appropriate communication (Office of Minority Health, 2021), including communication that is accessible to persons with disabilities, and ensure access to an appropriate, affordable, diversified, coordinated, and effective nonpharmacologic and pharmacologic pain management regimen for all persons.

Determining whether or not to initiate opioids for pain

All patients with pain should receive treatment that provides the greatest benefits relative to risks. See Recommendation 1 for determining whether to initiate opioids for acute pain (i.e., with a duration of less than one month) and Recommendation 2 for determining whether or not to initiate opioids for subacute (i.e., with a duration of at least one month and less than three months) or chronic pain (i.e., with a duration of three months or more).

1. **Nonopioid therapies are effective for many common types of acute pain. Clinicians should only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient (recommendation category: B, evidence type: 3).**

Implementation considerations:

- *There is an important role for opioid therapy for acute pain related to severe traumatic injuries (including crush injuries and burns), invasive surgeries typically associated with moderate to severe postoperative pain, and other severe acute pain when NSAIDs and other therapies are contraindicated or likely to be ineffective.*

- *Opioids are not first-line therapy for many common acute pain conditions, including low back pain, neck pain, pain related to other musculoskeletal injuries (such as sprains, strains, tendonitis, bursitis), pain related to minor surgeries typically associated with minimal tissue injury and only mild postoperative pain (e.g., dental extraction), dental pain, kidney stone pain, and headaches including episodic migraine.*

- *When diagnosis and severity of acute pain are reasonably assumed to warrant the use of opioids, clinicians should prescribe immediate-release opioids (see Recommendation 3) at the lowest dose to achieve expected effects (see Recommendation 4) and for no longer than the expected duration of pain severe enough to require opioids (see Recommendation 6).*

- *Clinicians should maximize use of nonopioid pharmacologic (e.g., NSAIDs and/or acetaminophen) and nonpharmacologic (e.g., ice, heat, elevation, rest, immobilization and/or exercise) therapies as appropriate for the specific condition and continue these therapies as needed once opioids are discontinued.*

- *Clinicians should prescribe and advise opioid use only as needed (e.g., hydrocodone 5 mg/acetaminophen 325mg, one tablet not more frequently than every 4 hours as needed for pain) rather than on a scheduled basis (e.g., one tablet every 4 hours) and encourage and include an opioid taper if opioids will be taken around the clock for more than a few days (see Recommendation 6).*

- *If patients already receiving opioids in a long-term fashion require additional medication for acute pain, nonopioid medications should be used when possible, and if additional opioids are*

required (e.g., for superimposed severe acute pain), they should be continued only for the duration of pain severe enough to require additional opioids, returning to the patient's baseline opioid dosage as soon as possible, including a taper to baseline dosage if additional opioids were used around the clock for more than a few days (see Recommendation 6).

- *Clinicians should ensure that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients meaningfully in decisions about whether to start opioid therapy.*

Supporting Rationale

Evaluation of the patient is critical in order to inform appropriate management. Evaluation can identify reversible causes of pain and underlying etiologies with potentially serious sequelae that require urgent action. To guide patient-specific selection of therapy, clinicians should evaluate patients and establish or confirm the diagnosis. Diagnosis can help identify interventions to reverse, ameliorate, or prevent worsening of pain and improve function; for example, surgical intervention to repair structure and function following certain traumatic injuries, bracing to prevent recurrence of acute ankle sprain, fracture immobilization, ice or elevation to reduce swelling, and early mobilization to maintain function (Doherty, Bleakley, Delahunt, & Holden, 2017).

Noninvasive, nonpharmacologic approaches to acute pain

Noninvasive, nonpharmacologic approaches have the potential to improve pain and function without risk of serious harms (Chou et al., December 2020). The clinical evidence reviews found that some nonpharmacologic treatments were likely effective for acute pain (e.g., heat therapy will probably be effective for acute low back pain, spinal manipulation might be effective for acute back pain with radiculopathy, a cervical collar or exercise might be effective for acute neck pain with radiculopathy, acupressure might be effective for acute musculoskeletal pain, massage might be effective for postoperative pain (Chou et al., December 2020), and remote electrical neuromodulation might improve acute pain related to episodic migraine (Halker Singh et al., December 2020)). Some nonpharmacologic

therapies are relatively low cost and available without a clinician appointment (e.g., heat for low back pain) (Chou et al., December 2020).

The American College of Physicians recommends nonpharmacologic treatment with superficial heat, massage, acupuncture, or spinal manipulation as a cornerstone of treatment for acute low back pain (Qaseem, Wilt, McLean, & Forciea, 2017). The American College of Physicians and American Academy of Family Physicians suggest acupressure to improve pain and function and transcutaneous electrical nerve stimulation to reduce pain in patients with acute musculoskeletal injuries (Qaseem et al., 2020).

Despite evidence supporting their use, noninvasive, nonpharmacologic therapies are not always or fully covered by insurance (Heyward et al., 2018), and access and cost can be barriers for patients, particularly for patients who are uninsured, individuals with limited income, and for people with transportation challenges or living in rural areas. Experts expressed concern about limited access to non-opioid pain management modalities, in part due to lack of availability or lack of coverage by payers, and emphasized improving access to non-opioid pain management modalities as a priority. To improve pain management and reduce medication use and associated risks, health insurers and health systems should increase access to noninvasive, nonpharmacologic therapies with evidence of effectiveness. Noninvasive, nonpharmacologic approaches should be used as appropriate to alleviate acute pain, including ice and elevation to reduce swelling and discomfort from musculoskeletal injuries, heat to alleviate low back pain, and other modalities depending on the cause of the acute pain.

Nonopioid medications for acute pain

Many acute pain conditions can often be managed most effectively with nonopioid medications (Chou et al., December 2020). NSAIDs are probably more effective than opioids for surgical dental pain and for kidney stone pain and similarly effective to opioids for low back pain (Chou et al., December 2020). There is limited evidence on comparative effectiveness of therapies for acute neuropathic pain,

neck pain, and postoperative pain (Chou et al., December 2020). For episodic migraine, triptans, NSAIDs, antiemetics, dihydroergotamine, CGRP antagonists, and lasmiditan are associated with improved pain and function with generally mild and transient adverse events (Halker Singh et al., December 2020).

The American College of Physicians recommends NSAIDs or skeletal muscle relaxants if pharmacologic treatment is desired to treat low back pain (Qaseem et al., 2017). For acute musculoskeletal injuries other than low back pain, the American College of Physicians and American Academy of Family Physicians recommend topical NSAIDs with or without menthol gel as first-line therapy and suggest oral NSAIDs to improve function, or oral acetaminophen to reduce pain (Qaseem et al., 2020). The American Dental Association recommends NSAIDs as first-line treatment for acute dental pain management (American Dental Association, 2020). For pain management for women in the postpartum period, the American College of Obstetricians and Gynecologists (ACOG) recommends a stepwise, multimodal approach. After vaginal delivery, ACOG recommends acetaminophen or NSAIDs, and if needed, escalating to an opioid; after caesarian delivery, ACOG recommends standard oral and parenteral medications such as acetaminophen, NSAIDs, and/or low-dose, low-potency, short-acting opioids with duration of opioid use limited to the shortest reasonable course expected for treating acute pain (The American College of Obstetricians and Gynecologists, 2021). ACOG recommends counseling individuals who are prescribed opioids about the risk of central nervous system depression in the individual and in the breastfed infant (The American College of Obstetricians and Gynecologists, 2021). For acute kidney stone pain, NSAIDs are at least as effective as opioids (Cordell et al., 1994; Cordell et al., 1996; Teichman, 2004; Udén, Rentzhog, & Berger, 1983), can decrease the ureteral smooth muscle tone and ureteral spasm (Cole, Fry, & Shuttleworth, 1988) causing kidney stone pain, and are preferred for kidney stone pain if not contraindicated. Triptans, NSAIDs, combined triptans with NSAIDs, as well as antiemetics, dihydroergotamine, and acetaminophen are established acute treatments for migraine (Halker Singh et al., December 2020). The 5-HT1F receptor antagonist lasmiditan and the gepant

ubrogepant were approved by the FDA in 2019 for the treatment of migraine (U.S. Food and Drug Administration, 2019a); another gepant, rimegepant, was approved in 2020. Lasmiditan and the gepants were more effective than placebo in providing pain relief at 2 hours, 1 day, and at 1 week (Halker Singh et al., December 2020). Adverse events related to these newer medications require further study, but given their mechanisms of action, are believed to be nonvasoconstrictive (Shapiro et al., 2019), and potentially carry lower risks than vasoactive medications in patients with cardiovascular risk factors (Halker Singh et al., December 2020).

When not contraindicated, NSAIDs should be used for low back pain, painful musculoskeletal injuries (including minor pain related to fractures), dental pain, postoperative pain, and kidney stones; triptans, NSAIDs, or their combinations should be used along with antiemetics as needed for acute pain related to episodic migraine. NSAID use has been associated with serious gastrointestinal events and major coronary events (McDonagh et al., April 2020), particularly in patients with cardiovascular or gastrointestinal co-morbidities, and clinicians should weigh risks and benefits of use, dose, and duration of NSAIDs when treating older adults as well as patients with hypertension, renal insufficiency, or heart failure, or those with risk for peptic ulcer disease or cardiovascular disease. Vasoactive effects of triptans and ergot alkaloids might preclude their use in patients with migraine who also have cardiovascular risk factors (Buse, Reed, Fanning, Kurth, & Lipton, 2017; Halker Singh et al., December 2020; Lipton, Reed, Kurth, Fanning, & Buse, 2017). Clinicians should review FDA-approved labeling, including boxed warnings before initiating treatment with any pharmacologic therapy.

Opioid medication for acute pain

The evidence review (Chou et al., December 2020) found that opioids might not be more effective than nonopioid therapies for some acute pain conditions (Chang, Bijur, Esses, Barnaby, & Baer, 2017; Friedman et al., 2015; Lewis et al., 2015; Moore & Hersh, 2013; Pathan, Mitra, & Cameron, 2018),

and use of opioids might negatively affect recovery and function (Franklin, Stover, Turner, Fulton-Kehoe, & Wickizer, 2008; B. S. Webster, Verma, & Gatchel, 2007). The review found that opioids were probably less effective than NSAIDs for surgical dental pain and kidney stones, less effective than acetaminophen for kidney stone pain, and similarly effective as NSAIDs for low back pain (Chou et al., December 2020). For postoperative pain, effects of opioids on pain intensity were inconsistent, and opioids were associated with increased likelihood of repeat or rescue analgesic use (Chou et al., December 2020). There was some evidence that opioids might be more effective than gabapentin for acute neuropathic pain (Chou et al., December 2020). There was insufficient evidence for opioids in treatment of episodic migraine (Halker Singh et al., December 2020). Compared with NSAIDs or acetaminophen, opioids were associated with increased risk of short-term adverse events, including any adverse event, nausea, dizziness, and somnolence (Chou et al., December 2020). Observational studies found opioid use for acute low back pain or postoperative pain was associated with increased likelihood of long-term opioid use (Chou et al., December 2020). Proportions of adults with new long-term opioid use at follow-up after initiation for short-term use for post-operative pain have ranged from <1% to 13% (Brummett et al., 2017; Deyo et al., 2018; Goesling et al., 2016; S. P. Johnson et al., 2016; J. S. Lee et al., 2017; E. C. Sun, Darnall, Baker, & Mackey, 2016). Odds of long-term opioid use at follow-up after initiation for short-term use for acute pain might be greater with higher dose and duration of exposure. For example, one study found that compared with no early opioid use for acute low back pain, the adjusted odds ratio was 2.08 (95% CI 1.55 to 2.78) for an early prescription totaling 1 to 140 MME/day and increased to 6.14 (95% CI 4.92 to 7.66) for an early prescription totaling ≥450 MME/day (B. S. Webster et al., 2007). In episodic migraine, opioids as well as butalbital-containing medications were associated with a two-fold higher risk of development of medication overuse headache compared with simple analgesics and triptans (Halker Singh et al., December 2020; Katsarava et al., 2004). Serious adverse events were

uncommon for opioids as well as for other medications, but studies were not designed to assess risk of overdose, opioid use disorder, or long-term harms (Chou et al., December 2020).

For acute low back pain, the American College of Physicians found insufficient evidence for effectiveness of opioids and recommends nonopioid medications (see **Nonopioid medications for acute pain**) if choosing pharmacologic treatment (Qaseem et al., 2017). The American College of Physicians and American Academy of Family Physicians suggest against treating patients with acute pain from musculoskeletal injuries with opioids, including tramadol (Qaseem et al., 2020). The American Dental Association recommends NSAIDs as the first-line therapy for acute pain management (see **Nonopioid medications for acute pain**) (American Dental Association, 2020). The American College of Obstetricians and Gynecologists recommends a shared decision-making approach to postpartum discharge pain management, incorporating pharmacologic treatments that may include opioids, limiting duration of opioid use to the shortest reasonable course expected for treating acute pain, noting that if a codeine-containing medication is selected, duration of therapy and neonatal signs of toxicity should be reviewed with individuals and their families (The American College of Obstetricians and Gynecologists, 2021). Multiple guidelines addressing prescribing for postoperative pain include both nonopioid and opioid treatment options and have emphasized multimodal analgesia, incorporating around the clock nonopioid analgesics and nonpharmacologic therapies and noting that systemic opioids are often needed postoperatively but are not required in all patients (Chou et al., 2016; Hill, Stucke, Billmeier, Kelly, & Barth, 2018; Overton et al., 2018). The American Headache Society recommends against prescribing opioid or butalbital-containing medications as first-line treatment for recurrent headache disorders (Loder, Weizenbaum, Frishberg, & Silberstein, 2013), and the American Academy of Neurology recommends against use of these medications for treatment of migraine, except as a last resort (Langer-Gould et al., 2013).

Given equivalent or lesser effectiveness for pain relief compared with NSAIDs and risks of long-term opioid use after using opioids for acute pain, opioids are not recommended as first-line therapy for many common acute pain conditions, including low back pain, neck pain, pain related to other musculoskeletal injuries (such as sprains, strains, tendonitis, bursitis), pain related to minor surgeries typically associated with minimal tissue injury and only mild postoperative pain (e.g., dental extraction), dental pain, kidney stone pain, and headaches including episodic migraine. There is an important role for opioid therapy for acute pain related to severe traumatic injuries (including crush injuries and burns), invasive surgeries typically associated with moderate to severe postoperative pain, and other severe acute pain when NSAIDs and other therapies are contraindicated or likely to be ineffective.

When diagnosis and severity of acute pain are reasonably assumed to warrant the use of opioids, clinicians should prescribe immediate-release opioids (see Recommendation 3) at the lowest dose to achieve expected effects (see Recommendation 4) and for no longer than the expected duration of pain severe enough to require opioids (see Recommendation 6) to minimize unintentional initiation of long-term opioid use. Clinicians should maximize use of nonopioid pharmacologic (e.g., NSAIDs and/or acetaminophen) and nonpharmacologic (e.g., ice, heat, elevation, rest, immobilization and/or exercise) therapies as appropriate for the specific condition and continue these therapies as needed once opioids are discontinued. Clinicians should work with patients to prevent prolonged opioid use, prescribe and advise opioid use only as needed (e.g., hydrocodone 5 mg/acetaminophen 325mg, one tablet not more frequently than every 4 hours as needed for pain) rather than on a scheduled basis (e.g., one tablet every 4 hours), and encourage and include an opioid taper if opioids will be taken around the clock for more than a few days (see Recommendation 6). Clinicians should consider concurrent medical conditions, including sleep apnea, pregnancy, renal or hepatic insufficiency, mental health conditions, and substance use disorder, in assessing risks of opioid therapy (see Recommendation 8), offer naloxone if the patient or a household member has risk factors for opioid overdose (see Recommendation 8), use

extreme caution when prescribing benzodiazepines or other sedating medications with opioids (see Recommendation 11), and check the PDMP database to ensure a new opioid prescription will not contribute to cumulative opioid dosages or medication combinations that put the patient at risk for overdose (see Recommendation 9). If there are signs of opioid use disorder, clinicians should address concerns with the patient, should offer or arrange medication treatment for patients who meet criteria for opioid use disorder, and should use nonpharmacologic and pharmacologic treatments as appropriate to manage the patient's pain (see Recommendation 12 and The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update (American Society of Addiction Medicine, 2020)).

Although findings regarding risks of new long-term opioid use after use for acute pain (Chou et al., December 2020) relate specifically to patients who were previously opioid-naïve, there might also be risks associated with dose escalation (see Recommendation 4) if patients already treated with long-term opioids are prescribed additional opioid medication for new acute pain superimposed on chronic pain. Therefore, strategies that minimize opioid use should be implemented for both opioid-naïve and opioid-tolerant patients with acute pain when possible. If patients already receiving long-term opioids require additional medication for acute pain, nonopioid medications should be used when possible, and if additional opioids are required (e.g., for superimposed severe acute pain), they should be continued only for the duration of pain severe enough to require additional opioids, returning to the patient's baseline opioid dosage as soon as possible, including an appropriate taper to baseline dosage if additional opioids were used around the clock for more than a few days (see Recommendation 6).

Patient education and discussion before starting outpatient opioid therapy are critical so that patient preferences and values can be understood and inform clinical decisions. Clinicians should ensure that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients in decisions about whether to

start opioid therapy. Essential elements for communication and discussion with patients before starting outpatient opioid therapy for acute pain include the following:

- Advise patients that short-term opioid use can lead to unintended long-term opioid use and the importance of working toward planned discontinuation of opioid use as soon as feasible, including a plan to appropriately taper opioids as pain resolves if opioids have been used around the clock for more than a few days (see Recommendation 6).
- Review communication mechanisms and protocols patients can use to inform clinicians of severe or uncontrolled pain and to arrange for timely reassessment and management.
- Advise patients about serious adverse effects of opioids, including potentially fatal respiratory depression and development of a potentially serious lifelong opioid use disorder (see Recommendation 12) that can cause distress and inability to fulfill major role obligations at work, school, or home.
- 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. To prevent constipation associated with opioid use, advise patients to increase hydration and fiber intake and to maintain or increase physical activity as they are able. A cathartic (e.g., senna) with or without a stool softener or a laxative might be needed if opioids are used for more than a few days. To minimize withdrawal symptoms, clinicians should provide and discuss an opioid tapering plan when opioids will be used around the clock for more than a few days (see Recommendation 6). Limiting opioid use to the minimum needed to manage pain (e.g., taking the opioid only when needed if needed less frequently than every 4 hours and the prescription is written for every 4 hours as needed for pain) can help limit development of tolerance and therefore of withdrawal once opioids are discontinued.

- If formulations are prescribed that combine opioids with acetaminophen, advise patients of the risks of taking additional over-the-counter products containing acetaminophen. Acetaminophen can be hepatotoxic at dosages of >3–4 grams/day and at lower dosages in patients with chronic alcohol use or liver disease (American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009).
- To help patients assess when a dose of opioids is needed, explain that the goal is to reduce pain to make it manageable rather than to eliminate pain.
- Discuss effects that opioids might have on ability to safely operate a vehicle or other machinery, particularly when opioids are initiated 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, i.e., not taking more opioids or taking them more often.
- Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, non-prescribed or illicit drugs such as heroin, or other opioids (see Recommendations 8, 11).
- 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 and pets are susceptible to unintentional ingestion. Discuss storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids (U.S. Food and Drug Administration, 2020a).

- Discuss planned use of precautions to reduce risks, including naloxone for overdose reversal (see Recommendation 8), and clinician use of prescription drug monitoring program information (see Recommendation 9).

2. Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks (recommendation category: A, evidence type: 2).

Implementation considerations:

- *To guide patient-specific selection of therapy, clinicians should evaluate patients and establish or confirm the diagnosis.*
- *Clinicians should use appropriate noninvasive, nonpharmacologic approaches to help manage chronic pain, such as exercise (aerobic, aquatic, and/or resistance exercises) or exercise therapy (a prominent modality in physical therapy) for back pain, fibromyalgia, and hip or knee osteoarthritis; weight loss for knee osteoarthritis; manual therapies for hip osteoarthritis; psychological therapy, spinal manipulation, low-level laser therapy, massage, mindfulness-based stress reduction, yoga, acupuncture, and multidisciplinary rehabilitation for low back pain; mind-body practices (yoga, tai chi, qigong), massage, and acupuncture for neck pain; CBT, myofascial release massage, mindfulness practices, tai chi, qigong, acupuncture, and multidisciplinary rehabilitation for fibromyalgia; and spinal manipulation for tension headache.*
- *Low-cost options to integrate exercise include walking in public spaces or use of public recreation facilities for group exercise. Physical therapy can be helpful, particularly for patients who have limited access to safe public spaces or public recreation facilities for exercise or have not improved with low-intensity physical exercise.*
- *To improve pain management and reduce medication use and associated risks, health insurers and health systems should increase access to noninvasive, nonpharmacologic therapies with evidence for effectiveness.*
- *Clinicians should review FDA-approved labeling including boxed warnings and weigh benefits and risks before initiating treatment with any pharmacologic therapy.*

- *When patients affected by osteoarthritis have an insufficient response to nonpharmacologic interventions such as exercise for arthritis pain, topical NSAIDs can be used in patients with a single or few joints near the surface of the skin (e.g., knee). In patients with osteoarthritis pain in multiple joints or incompletely controlled with topical NSAIDs, duloxetine or systemic NSAIDs can be considered.*

- *NSAIDs should be used at the lowest dose and duration needed and should be used with caution, particularly in patients with cardiovascular comorbidities, chronic renal failure, or previous gastrointestinal bleeding.*

- *When patients with chronic low back pain have had an insufficient response to nonpharmacologic approaches such as exercise, clinicians can consider NSAIDs or duloxetine for patients without contraindications.*

- *Tricyclic, tetracyclic, and SNRI antidepressants, selected anticonvulsants (pregabalin, gabapentin enacarbil, oxcarbazepine), and capsaicin and lidocaine patches can be considered for neuropathic pain.*

- *Duloxetine and pregabalin are FDA-approved for the treatment of diabetic peripheral neuropathy, and pregabalin and gabapentin are FDA-approved for treatment of post-herpetic neuralgia.*

- *In patients with fibromyalgia, tricyclic (amitriptyline) and SNRI antidepressants (duloxetine and milnacipran), NSAIDs (topical diclofenac), and specific anticonvulsants (pregabalin and gabapentin) are used to improve pain, function, and quality of life. Duloxetine, milnacipran, and pregabalin are FDA-approved for the treatment of fibromyalgia.*

- *Patients with co-occurring pain and depression might be especially likely to benefit from antidepressant medication (see Recommendation 8).*

- *Opioids should not be considered first-line or routine therapy for subacute or chronic pain. This does not mean that patients should be required to sequentially "fail" nonpharmacologic and nonopioid pharmacologic therapy or be required to use any specific 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 (e.g., 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. In other situations, (e.g., headache or fibromyalgia), expected benefits of initiating opioids are unlikely to outweigh risks regardless of previous nonpharmacologic and nonopioid pharmacologic therapies used.*

- *Opioid therapy should not be initiated without consideration by the clinician and patient of an "exit strategy" to be used if opioid therapy is unsuccessful.*

- *Before opioid therapy is initiated for subacute or chronic pain, clinicians should determine jointly with patients how effectiveness will be evaluated and establish treatment goals.*

- *Clinicians seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy. Clinicians should avoid rapid tapering or abrupt discontinuation of opioids (see Recommendation 5).*

- *Patient education and discussion before starting opioid therapy are critical so that patient preferences and values can be understood and used to inform clinical decisions.*

- *Clinicians should review available low-cost options for pain management for all patients, and particularly for low-income, underinsured and uninsured patients.*

- *Clinicians should ensure that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients in decisions about whether to start opioid therapy.*

Supporting Rationale

To guide patient-specific selection of therapy, clinicians should evaluate patients and establish or confirm the diagnosis. Detailed recommendations on diagnosis are provided in other guidelines (American College of Occupational and Environmental Medicine, 2017; Chou et al., 2007; Federation of State Medical Boards, 2017; Hooten et al., 2013; U.S. Department of Veterans Affairs and Department of Defense, 2017), but evaluation should generally include a focused history, including history and characteristics of pain and potential contributing factors (e.g., function, psychosocial stressors, sleep) and physical exam, with imaging or other diagnostic testing only if indicated (e.g., if severe or progressive neurologic deficits are present or if serious underlying conditions are suspected [Chou et al., 2007; Hooten et al., 2013]). For complex pain syndromes, pain specialty consultation can be considered to assist with diagnosis as well as management.

Diagnosis can help identify disease-specific interventions to reverse, ameliorate, or prevent worsening of pain and improve function; for example, improving glucose control to prevent progression of diabetic neuropathy; immune-modulating agents for rheumatoid arthritis; physical or occupational therapy to address posture, muscle weakness, or repetitive occupational motions that contribute to musculoskeletal pain; or surgical intervention to relieve mechanical/compressive pain (Hooten et al., 2013). The underlying mechanism for most pain syndromes can be categorized as neuropathic (e.g.,

diabetic neuropathy, postherpetic neuralgia, fibromyalgia), or nociceptive (e.g., osteoarthritis, muscular back pain). The diagnosis and pathophysiologic mechanism of pain have implications for symptomatic pain treatment with medication. For example, there is limited evidence for improved pain or function, or evidence of worse outcomes, with long-term use of opioids for several chronic pain conditions for which opioids are commonly prescribed, such as osteoarthritis (Bannuru et al., 2019), low back pain (Chaparro et al., 2014; Qaseem et al., 2017), headache (Loder et al., 2013), and fibromyalgia (Gaskell, Moore, Derry, & Stannard, 2014; Goldenberg, Clauw, Palmer, & Clair, 2016). For moderate to severe chronic back pain or hip or knee osteoarthritis pain, a nonopioid strategy starting with acetaminophen or NSAIDs results in significantly improved pain intensity compared to a strategy starting with opioids (E. E. Krebs et al., 2018). Tricyclic antidepressants, SNRI antidepressants, selected anticonvulsants, or transdermal lidocaine are recommended for neuropathic pain syndromes (e.g., diabetic neuropathy, postherpetic neuralgia [American College of Occupational and Environmental Medicine, 2017]).

In addition, review of the patient's history and context beyond the presenting pain syndrome is helpful in selection of pain treatments. In particular, medications should be used only after assessment and determination that expected benefits outweigh risks given patient-specific factors. For example, clinicians should consider fall risk when selecting and dosing potentially sedating medications such as tricyclics, anticonvulsants, and opioids, and should weigh risks and benefits of use, dose, and duration of NSAIDs when treating older adults as well as patients with hypertension, renal insufficiency, or heart failure, or those with risk for peptic ulcer disease or cardiovascular disease. Some guidelines recommend topical NSAIDs for localized osteoarthritis (e.g., knee osteoarthritis) over oral NSAIDs in patients aged ≥75 years to minimize systemic effects (Hochberg et al., 2012). See Recommendation 8 for additional considerations for assessing risks of opioid therapy.

Noninvasive, nonpharmacologic approaches to subacute and chronic pain

Many noninvasive, nonpharmacologic approaches, including physical therapy, weight loss for knee osteoarthritis, and psychological therapies such as CBT, and mindfulness-based stress reduction can improve pain and function without risk for serious harms (Skelly et al., April 2020). There is high-quality evidence that exercise therapy (a prominent modality in physical therapy) for back pain, fibromyalgia, and hip or knee osteoarthritis reduces pain and improves function immediately after treatment and that the improvements are sustained for at least 2–6 months (Busch, Barber, Overend, Peloso, & Schachter, 2007; Fransen et al., 2015; Fransen, McConnell, Hernandez-Molina, & Reichenbach, 2014; Hayden, van Tulder, Malmivaara, & Koes, 2005; Skelly et al., April 2020). Previous guidelines have recommended aerobic, aquatic, and/or resistance exercises for people with chronic pain, including osteoarthritis of the knee or hip, back pain, and fibromyalgia (American College of Occupational and Environmental Medicine, 2017; Hochberg et al., 2012; Macfarlane et al., 2017; Qaseem et al., 2017; U.S. Department of Veterans Affairs and Department of Defense, 2017). Other noninvasive, nonpharmacologic therapies that improve pain and/or function for at least one month after delivery without apparent risk for serious harm include CBT for knee osteoarthritis; manual therapies for hip osteoarthritis; psychological therapy, spinal manipulation, low-level laser therapy, massage, mindfulness-based stress reduction, yoga, acupuncture, and multidisciplinary rehabilitation for low back pain; mind-body practices (e.g., yoga, tai chi, qigong), massage, and acupuncture for neck pain; CBT, myofascial release massage, mindfulness practices, tai chi, qigong, acupuncture, and multidisciplinary rehabilitation for fibromyalgia; and spinal manipulation for tension headache (Skelly et al., April 2020). For temporomandibular disorder pain, patient education and self-care can be effective, as can occlusal splints for some patients and biobehavioral therapy for prevention of disabling symptoms (List & Axelsson, 2010; Michelotti, Iodice, Vollaro, Steenks, & Farella, 2012). Exercise, mind-body interventions, and psychological treatments (including CBT and mindfulness practices) can encourage active patient participation in the care plan and address the effects of pain in the patient's life; these more "active"

therapies have somewhat more robust evidence for sustained improvements in pain and function than more "passive" treatments (e.g., massage), particularly at longer-term follow-up (Skelly et al., April 2020). Active approaches that engage the patient should be used, when possible, with a supplementary role for more passive approaches, to reduce pain and improve function.

Despite their favorable benefit-to-risk profile, noninvasive, nonpharmacologic therapies are not always or fully covered by insurance (Heyward et al., 2018). Access and cost can be barriers for patients, particularly people who are low-income, uninsured, underinsured, or living in rural areas or with transportation challenges. To improve pain management and reduce medication use and associated risks, health insurers and health systems should increase access to noninvasive, nonpharmacologic therapies with evidence for effectiveness. In addition, for many patients, aspects of these approaches can be used even when there is limited access to specialty care. For example, previous guidelines have strongly recommended aerobic, aquatic, and/or resistance exercises for patients with osteoarthritis of the knee or hip (Hochberg et al., 2012) and maintenance of physical activity, including normal daily activities, for patients with low back pain (Chou et al., 2007). A randomized trial found no difference in reduced chronic low back pain intensity, frequency or disability between patients assigned to relatively low-cost group aerobics and individual physiotherapy or muscle reconditioning sessions (Mannion, Müntener, Taimela, & Dvorak, 1999). Low-cost options to integrate exercise include walking in public spaces or use of public recreation facilities for group exercise. Physical therapy can be helpful, particularly for patients who have limited access to safe public spaces or public recreation facilities for exercise or have not improved with low-intensity physical exercise. A randomized trial found a stepped exercise program, in which patients were initially offered an internet-based exercise program and progressively advanced to biweekly coaching calls and then to in-person physical therapy if not improved at previous steps, successfully improved symptomatic knee osteoarthritis, with 35% of patients ultimately requiring in-person physical therapy (Allen et al., 2020). In addition, primary care

clinicians can integrate elements of psychosocial therapies such as CBT, which addresses psychosocial contributors to pain and improves function (A. C. Williams, Eccleston, & Morley, 2012), by encouraging patients to take an active role in the care plan, by supporting patients in engaging activities such as exercise that are generally beneficial but that might initially be associated with fear of exacerbating pain (Hooten et al., 2013), or by providing education in relaxation techniques and coping strategies. In many locations, there are free or low-cost patient support, self-help, and educational community-based or employer-sponsored programs that can provide stress reduction and other mental health benefits. Clinicians should be familiar with such options within their communities so they can refer patients to low-cost services. Patients with higher levels of anxiety or fear related to pain, or other significant psychological distress, can be referred for treatment with a mental health specialist (e.g., psychologist, psychiatrist, clinical social worker).

Nonopioid medications for subacute and chronic pain

Several nonopioid pharmacologic therapies (including acetaminophen, NSAIDs, and selected antidepressants and anticonvulsants) are used for painful symptoms in chronic pain conditions. Nonopioid pharmacologic therapies are associated with risks, particularly in older adults, pregnant patients, and patients with certain co-morbidities such as cardiovascular, renal, gastrointestinal, and liver disease. For example, NSAID use has been associated with serious gastrointestinal events and major coronary events (McDonagh et al., April 2020). Increases in non-serious adverse events have been found with the anticonvulsants pregabalin (blurred vision, cognitive effects, sedation, weight gain, dizziness and peripheral edema) and gabapentin (blurred vision, cognitive effects, sedation, and weight gain), with cannabis (nausea and dizziness), and with the SNRIs duloxetine (nausea, sedation) and milnacipran (nausea); dose reductions reduced the risk of some adverse events with SNRI

antidepressants (McDonagh et al., April 2020). Clinicians should review FDA-approved labeling including boxed warnings before initiating treatment with any pharmacologic therapy.

For osteoarthritis, NSAIDs including topical NSAIDs (diclofenac) and the SNRI duloxetine have small to moderate benefits for pain and function at short-term assessment (3 to 6 months), with intermediate-term (6 to 12 months) evidence for some medications (celecoxib and duloxetine), and some evidence that duloxetine is more effective in older (>65 years) compared to younger patients and in patients with knee osteoarthritis (McDonagh et al., April 2020). Acetaminophen has limited evidence for effectiveness (McDonagh et al., April 2020) and is no longer considered a first-line treatment for osteoarthritis (Bannuru et al., 2019). When patients have an insufficient response to nonpharmacologic interventions such as exercise for arthritis pain and if a single or a few joints near the surface of the skin (e.g., knee) are affected by osteoarthritis, use of topical NSAIDs is recommended (Bannuru et al., 2019). In patients with osteoarthritis pain in multiple joints or incompletely controlled with topical NSAIDs, systemic NSAIDs or duloxetine can be used. However, systemic NSAIDs should be used at the lowest dose and duration needed as risks may increase with longer use and at higher doses (U.S. Food and Drug Administration, 2015b). NSAIDs should be used with caution particularly in patients with cardiovascular comorbidities, chronic renal failure, or previous gastrointestinal bleeding. In patients with gastrointestinal comorbidities but without current or previous gastrointestinal bleeding, cyclooxygenase-2 (COX-2) inhibitors or NSAIDs with proton pump inhibitors can be used to minimize risk compared to risk with use of NSAIDs alone (Bannuru et al., 2019). Moderate-quality evidence shows small improvements in chronic low back pain with NSAIDs (Qaseem et al., 2017) and with duloxetine (McDonagh et al., April 2020). When patients have had an insufficient response to nonpharmacologic approaches such as exercise, clinicians can consider NSAIDs or duloxetine (Qaseem et al., 2017) for patients without contraindications. For temporomandibular disorder pain that is not sufficiently improved with nonpharmacologic interventions, NSAIDs can be effective (Kulkarni, Thambar, & Arora,

2020; Mujakperuo, Watson, Morrison, & Macfarlane, 2010). Tricyclic, tetracyclic, and SNRI antidepressants, selected anticonvulsants, and capsaicin and lidocaine patches are recommended for neuropathic pain (American College of Occupational and Environmental Medicine, 2017). However, evidence on topical lidocaine and capsaicin is limited (McDonagh et al., April 2020). The SNRI antidepressant duloxetine and selected anticonvulsants (pregabalin, gabapentin enacarbil, oxcarbazepine) are associated with small improvements in neuropathic pain (mainly diabetic neuropathy and post-herpetic neuralgia) (McDonagh et al., April 2020). Duloxetine and pregabalin are FDA-approved for the treatment of diabetic neuropathy, and pregabalin and gabapentin are FDA-approved for treatment of post-herpetic neuralgia. In patients with fibromyalgia, several medications have been shown to be associated with small to moderate improvements in pain, function, and quality of life, including SNRI antidepressants (duloxetine and milnacipran), NSAIDs (topical diclofenac), and specific anticonvulsants (pregabalin and gabapentin) (McDonagh et al., April 2020). Tricyclics and SNRIs can also relieve fibromyalgia symptoms. Duloxetine, milnacipran, and pregabalin are FDA-approved for and are recommended for the treatment of fibromyalgia (American College of Occupational and Environmental Medicine, 2017). The tricyclic antidepressant amitriptyline is often used and recommended in patients with fibromyalgia (American College of Occupational and Environmental Medicine, 2017), although evidence on its effectiveness is limited (McDonagh et al., April 2020). Because patients with chronic pain might experience concurrent depression (Howe & Sullivan, 2014), and depression can exacerbate physical symptoms including pain (Sullivan, Edlund, Zhang, Unützer, & Wells, 2006), patients with co-occurring pain and depression might be especially likely to benefit from antidepressant medication (see Recommendation 8). Evidence on effectiveness of cannabis for painful conditions is limited, inconsistent across studies, and some studies have reported adverse events such as dizziness, nausea, and sedation (Banerjee & McCormack, 2019; McDonagh et al., April 2020).

Opioid medication for subacute and chronic pain

The clinical evidence reviews found insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and found an increased risk for serious harms related to long-term opioid therapy that appears to be dose-dependent (Chou et al., April 2020). Compared with no opioid use, opioid use was associated with increased risk of opioid use disorder, overdose, all-cause mortality, fractures, falls, and myocardial infarction (Chou et al., April 2020). Opioids were also associated with increased risk of discontinuation due to gastrointestinal adverse events, somnolence, dizziness, and pruritus (Chou et al., April 2020). Compared with placebo, at short-term (1 - <6 months) follow-up, opioids were associated with small mean improvements in pain intensity (mean difference -0.79 point on a 0 to 10 scale, 95% confidence interval [CI], -0.93 to -0.67, I2=71%) and function (Chou et al., April 2020). There was some evidence that improvement in pain is reduced with longer duration of opioid therapy; from a mean improvement of 1 on a 0 to 10 scale at 1 to 3 months to about 0.5 at 3 to 6 months (Chou et al., April 2020). No placebo-controlled trial evaluated effectiveness of opioids at intermediate (6 - <12 months) or long-term (≥12 months) follow-up (Chou et al., April 2020). Compared with nonopioid treatments at short-term follow-up, there were no differences in mean pain improvement (mean difference -0.29 on a 0 to 10 scale, 95% CI, -0.61 to 0.03) or functional improvement. No trials compared opioids with nonopioid therapies at intermediate or long-term follow-up, with the exception of one trial which found stepped therapy starting with opioids associated with higher pain intensity than stepped therapy starting with nonopioids (4.0 vs. 3.5, mean difference 0.5, 95% CI, 0.0 to 1.0) at 12-months (Chou et al., April 2020; E. E. Krebs et al., 2018).

The clinical evidence reviews identified an observational study (Edlund et al., 2014) finding long-term (>90 days' supply) opioid prescription to be associated with significantly increased risk of a new opioid use disorder diagnosis for all dosages of long-term (>90 days' supply) opioids prescribed, with adjusted odds ratios of 15, 29, and 122 at low (1 to 36 MME/day), medium (36 to 120 MME/day) and

high (≥120 MME/day) opioid dosages, respectively). Compared with no opioid use, opioid use was associated with increased risk of opioid use disorder, overdose, all-cause mortality, fractures, falls, and myocardial infarction (Chou et al., April 2020).

Several experts from the Opioid Workgroup appreciated the importance of highlighting both pain and function, of clinicians being realistic "upfront" with patients, and of attention to tapering and exit strategies. While some experts felt the recommendation statement could state nonopioid therapies "may be preferred" or "may be effective" for chronic pain, others agreed with language that nonopioid therapies "are preferred" for chronic pain, given opioid therapies are associated with small short-term benefits compared with placebo, comparable or reduced short-term benefits compared with nonopioid therapies, uncertain long-term benefits, and potential for serious harms.

Opioids should not be considered first-line or routine therapy for subacute or chronic pain. Although evidence on long-term benefits of nonopioid therapies is also limited, these therapies are also associated with short-term benefits, there is no evidence for attenuated benefit over time or difficulty stopping therapy when benefits do not outweigh risks, and risks for serious harms are usually lower. ***This does not mean that patients should be required to sequentially "fail" nonpharmacologic and nonopioid pharmacologic therapy*** *or be required to use any specific 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 (e.g., 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. In other situations (e.g., headache or fibromyalgia), expected benefits of initiating opioids are unlikely to outweigh risks regardless of previous nonpharmacologic and nonopioid pharmacologic therapies used.***

The clinical evidence reviews found no instrument with high accuracy for predicting opioid-related harms such as overdose or opioid use disorder (Chou et al., April 2020). It can be very challenging for clinicians to predict whether benefits of opioids for chronic pain will outweigh risks of ongoing treatment for individual patients. ***Therefore, opioid therapy should not be initiated without consideration by the clinician and patient of an "exit strategy" that could be used if opioid therapy is unsuccessful***. Before opioid therapy is initiated for subacute or chronic pain, clinicians should determine with patients how effectiveness will be evaluated and establish treatment goals. Some patients have reported treatment goals are effective in increasing motivation and functioning (Chou et al., April 2020). Goals ideally include improvement in pain relief, function (including social and emotional as well as physical dimensions), and quality of life. Goals can be tailored to individual patient and clinical circumstances. For example, for some patients with diseases typically associated with progressive functional impairment or catastrophic injuries such as spinal cord trauma, reductions in pain without improvement in physical function might be more realistic. Clinicians can assess and then follow (see Recommendation 7) function, pain control, and quality of life using tools such as the three-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale (Krebs et al., 2009). Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function (Ostelo et al., 2008). Clinicians can ask patients about functional goals that have meaning for them (e.g., walking the dog or walking around the block, returning to part-time work, attending family sports or recreational activities), and then use these goals in assessing benefits of opioid therapy for individual patients and in weighing benefits against risks of continued opioid therapy (see Recommendation 7). Clinicians seeing new patients already using opioid medication should establish treatment goals for continued opioid therapy. Clinicians should avoid rapid tapering or abrupt discontinuation of opioids (see Recommendation 5). Although the clinical evidence reviews did not find studies evaluating the effectiveness of written agreements or treatment plans (Chou et al., April 2020),

clinicians and patients who set a treatment plan in advance of prescribing will clarify expectations regarding how opioids will be prescribed and monitored with an aim to improve patient safety, health, and well-being.

Patient education and discussion before starting opioid therapy are critical so that patient preferences and values can be understood and used to inform clinical decisions. Clinicians should ensure that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients in decisions about whether to start opioid therapy. Many patients rank pain relief, nausea, vomiting, and constipation as significant effects (Chou et al., April 2020). Essential elements for communication and discussion with patients before starting opioid therapy include the following:

- Review available low-cost options for pain management for all patients, and particularly for low-income, underinsured, and uninsured patients. Review considerations related to access to care given the clinical oversight needed to initiate and continue opioid therapy and other treatments for pain.
- Be explicit and realistic about expected benefits of opioids, explaining that there is not robust evidence that opioids improve pain or function with long-term use, and that complete elimination of pain is unlikely.
- Emphasize improvement in function as a primary goal and that function can improve even when pain is not completely eliminated.
- Advise patients about serious adverse effects of opioids, including potentially fatal respiratory depression and development of a potentially serious lifelong opioid use disorder that can cause distress and inability to fulfill major role obligations at work, school, or home.
- 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. To prevent constipation associated with opioid use, advise patients to increase hydration and fiber intake and to maintain or increase physical activity. A cathartic (e.g., senna) with or without a stool softener or a laxative might be needed.

- If formulations are prescribed that combine opioids with acetaminophen, advise patients of the risks of taking additional over-the-counter products containing acetaminophen. Acetaminophen can be hepatotoxic at dosages of >3–4 grams/day and at lower dosages in patients with chronic alcohol use or liver disease (American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009).
- Discuss effects that opioids might have on ability to safely operate a vehicle or other machinery, 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, i.e., not taking more opioids or taking them more often.
- Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, non-prescribed 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 (U.S. Food and Drug Administration, 2020a).
- Discuss the importance of periodic reassessment to ensure that opioids are helping to meet patient goals and to allow opportunities for opioid dosage reduction and/or discontinuation and

consideration of additional nonpharmacologic or nonopioid pharmacologic treatment options if opioids are not effective or are harmful.

- Discuss expectations for clinician and patient responsibilities to mitigate risks of opioid therapy and planned use of precautions to reduce risks, including naloxone for overdose reversal (see Recommendation 8), and clinician use of prescription drug monitoring program information (see Recommendation 9) and toxicology screening (see Recommendation 10).
- Consider whether cognitive status might interfere with management of opioid therapy and, if so, determine whether a caregiver can responsibly co-manage medication therapy. Discuss the importance of reassessing medication use over time with both the patient and caregiver (as appropriate).

Given the possibility that benefits of opioid therapy might diminish or that risks might become more prominent over time, it is important that clinicians elicit patients' experiences and preferences and review expected benefits and risks of continued opioid therapy with patients periodically (see Recommendation 7).

Interventional approaches to subacute and chronic pain

Interventional approaches such as arthrocentesis and intraarticular glucocorticoid injection for pain associated with rheumatoid arthritis (Wallen & Gillies, 2006) or osteoarthritis (Bellamy et al., 2006) and subacromial corticosteroid injection for rotator cuff disease (Buchbinder, Green, & Youd, 2003) can provide short-term improvement in pain and function. Evidence is insufficient to determine the extent to which repeated glucocorticoid injection increases potential risks such as articular cartilage changes (in osteoarthritis) and sepsis (Bellamy et al., 2006). Interventional pain management specialists offer additional interventions that can alleviate pain as part of a comprehensive pain management approach

(U.S. Department of Health and Human Services, 2019b), including epidural steroid injections (for lumbar radiculopathy with herniated disc), nerve ablation procedures (e.g., radiofrequency denervation for low back pain), and neurostimulation procedures (e.g., peripheral nerve stimulation, spinal cord stimulation). Evidence is limited for many of these procedures, and additional research is needed to establish the clinical benefits of specific interventional procedures for specific pain conditions (Chou et al., 2021; U.S. Department of Health and Human Services, 2019b). Rare, serious adverse events have been reported with epidural injection (U.S. Food and Drug Administration, 2014c).

Multimodal therapy for subacute and chronic pain

Integrated pain management requires coordination of medical, psychological, and social aspects of healthcare and includes primary care, mental and behavioral healthcare, and specialist services when needed (The Interagency Pain Research Coordinating Committee, 2015). Multimodal therapies and multidisciplinary biopsychosocial rehabilitation-combining approaches (e.g., psychological therapies with exercise) can reduce long-term pain and disability compared with usual care and compared with physical treatments (e.g., exercise) alone. Nonpharmacologic therapies can also provide synergistic benefits when nonopioid or opioid pain medications are used (U.S. Department of Health and Human Services, 2019b). When needed, medications should ideally be combined with nonpharmacologic therapy to provide greater benefits to patients in improving pain and function. Multimodal therapies are not always available or reimbursed by insurance and can be time-consuming and costly for patients, and disparities for being able to access multimodal care exist. There is evidence that less-intensive multidisciplinary rehabilitation can be similarly effective to high-intensity multidisciplinary rehabilitation (Skelly et al., April 2020). Multimodal therapies should be considered for patients not responding to single-modality therapy, and combinations should be tailored depending on patient needs, cost, convenience, and other individual factors.

Depending on patient co-morbidities and benefit-to-risk ratio in individual patients, combinations of medications (for example, two nonopioid medications with different mechanisms of action or a nonopioid with an opioid medication) might also be used. In some cases, medication combinations might provide complementary or synergistic benefits and/or facilitate lower dosing of individual medications (Chou et al., April 2020), as has been demonstrated in trials of patients with neuropathic pain (Chou et al., April 2020). However, caution should be used to avoid synergistic risks of medications. For example, combinations of medications that depress the central nervous system and cause sedation (see Recommendation 11), such as an opioid with gabapentin, have been associated with increased risk of overdose compared with either medication alone (Chou et al., April 2020).

Opioid selection and dosage

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

Implementation considerations:

- *Clinicians should not treat acute pain with ER/LA opioids or initiate opioid treatment for subacute or chronic pain with ER/LA opioids, and clinicians should not prescribe ER/LA opioids for intermittent or as needed use.*
- *ER/LA opioids should be reserved for severe, continuous pain. Some ER/LA opioids should be considered only for patients who have received certain dosages of opioids (e.g., 60 mg daily of oral morphine, 30 mg daily of oral oxycodone, or equianalgesic dosages of other opioids) of immediate-release opioids daily for at least 1 week.*
- *When changing to an ER/LA opioid for a patient previously receiving a different immediate-release opioid, clinicians should consult product labeling and reduce total daily dosage to account for incomplete opioid cross-tolerance.*
- *Clinicians should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or hepatic dysfunction because decreased clearance of medications among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations.*

- *Although there might be situations in which clinicians need to prescribe immediate-release and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to immediate-release opioids by temporarily using lower dosages of both), in general, avoiding the use of immediate-release opioids in combination with ER/LA opioids is preferable, given the potential increased risk for adverse events, including respiratory depression and overdose.*

- *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 assessing risk for QT prolongation and considering electrocardiographic monitoring, should consider prescribing methadone for pain.*

- *Only clinicians who are familiar with the dosing and absorption properties of the ER/LA opioid transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.*

Supporting Rationale

ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of opioids such as oxycodone, hydromorphone, hydrocodone, and morphine. The clinical evidence reviews found effects of opioids on short-term pain and function were generally consistent across duration of action (short- or long-acting) and opioid type (opioid agonist, partial agonist, or mixed mechanism [with mixed opioid and nonopioid mechanisms of action] agent), although 5 trials directly comparing different types of opioids found a mixed mechanism agent associated with greater pain relief versus a pure opioid agonist, with fewer nonserious adverse events (Chou et al., April 2020). A fair-quality study showed a higher risk for overdose among patients treated with ER/LA opioids than among those treated with immediate-release opioids, especially within the first 2 weeks of therapy, with relative risk decreasing with longer duration of exposure (Chou et al., April 2020; Miller et al., 2015). The clinical evidence reviews did not find evidence that continuous, time-scheduled use of ER/LA opioids is more effective or safer than intermittent use of immediate-release opioids or that time-scheduled use of ER/ LA opioids reduces risks for opioid use disorder (Chou et al., April 2020). In 2014, the FDA modified the labeling for ER/LA opioid pain medications, noting serious risks and recommending that ER/LA opioids be reserved

for "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment" when "alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain" and not used as "as needed" pain relievers (U.S. Food and Drug Administration, 2013). FDA has also noted that some ER/LA opioids are only appropriate for opioid-tolerant patients, defined as patients who have received certain dosages of opioids (e.g., 60 mg daily of oral morphine, 30 mg daily of oral oxycodone, or equianalgesic dosages of other opioids) for at least 1 week (U.S. Food and Drug Administration, 2014b). Time-scheduled opioid use can be associated with greater total average daily opioid dosage compared with intermittent, as-needed opioid use (Von Korff et al., 2011). Abuse-deterrent technologies have been employed to prevent manipulation intended to defeat extended-release properties of ER/LA opioids and to prevent opioid use by unintended routes of administration, such as intravenous injection of oral opioids. As indicated in FDA guidance for industry on evaluation and labeling of abuse-deterrent opioids (U.S. Food and Drug Administration, 2015a), although abuse-deterrent technologies are expected to make manipulation of opioids more difficult or to reduce the potent effects of manipulation, they do not prevent opioid misuse or overdose through oral intake the most common route of opioid misuse — and can still be misused by nonoral routes. The "abuse-deterrent" label does not indicate that there is no risk for misuse or opioid use disorder. No studies were found in the clinical evidence reviews assessing the effectiveness of abuse-deterrent technologies as a risk mitigation strategy for deterring or preventing opioid misuse, use disorder, or overdose (Chou et al., April 2020). Experts agreed with the recommendation for clinicians to initiate opioid treatment with immediate-release opioids instead of with extended-release/long-acting (ER/LA) opioids and appreciated discussion of the lack of evidence for "abuse-deterrent" formulations.

In comparing different ER/LA formulations, the clinical evidence reviews found inconsistent results for overdose risk with methadone versus other ER/LA opioids used for chronic pain, with two

cohort studies of Medicaid beneficiaries finding methadone associated with increased risk of overdose or all-cause mortality versus morphine and one cohort study of Veterans Affairs patients finding methadone associated with decreased risk (Chou et al., April 2020). Methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for pain (Paulozzi, Mack, & Jones, 2012). In addition, methadone is associated with cardiac arrhythmias along with QT prolongation on the electrocardiogram, and it has complicated pharmacokinetics and pharmacodynamics, including a long and variable half-life and peak respiratory depressant effect occurring later and lasting longer than peak analgesic effect (Grissinger, 2011; Lugo, Satterfield, & Kern, 2005; Stringer, Welsh, & Tommasello, 2009). In regard to other ER/LA opioid formulations, the absorption and pharmacodynamics of transdermal fentanyl are also complex, with gradually increasing serum concentration during the first part of the 72-hour dosing interval, as well as variable absorption based on factors such as external heat. In addition, the dosing of transdermal fentanyl is in mcg/hour, which is not typical for a drug used by outpatients and can be confusing. These complexities might increase the risk for fatal overdose when methadone or transdermal fentanyl is prescribed.

Clinicians should not treat acute pain with ER/LA opioids or initiate opioid treatment for subacute or chronic pain with ER/LA opioids, and clinicians should not prescribe ER/LA opioids for intermittent use. Given longer half-lives and longer duration of effects (e.g., respiratory depression) with ER/LA opioids such as methadone, fentanyl patches, or extended-release versions of opioids such as oxycodone, hydromorphone, hydrocodone, or morphine, clinicians should not prescribe ER/LA opioids for the treatment of acute pain. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received certain dosages of immediate-release opioids daily (e.g., 60 mg daily of oral morphine, 30 mg daily of oral oxycodone, or equianalgesic dosages of other opioids) for at least 1 week. When changing to an ER/LA opioid for a patient previously receiving a different immediate-release opioid, clinicians should consult product labeling and reduce

total daily dosage to account for incomplete opioid cross-tolerance. Clinicians should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or hepatic dysfunction because decreased clearance of medications among these patients can lead to accumulation of medications to toxic levels and persistence in the body for longer durations. Although there might be situations in which clinicians need to prescribe immediate-release and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to immediate-release opioids by temporarily using lower dosages of both or in patients with opioid use disorder treated and stabilized on methadone who need short-acting opioids for acute pain), in general, avoiding the use of immediate-release opioids in combination with ER/LA opioids is preferable, given potentially increased risk.

When an ER/LA opioid is prescribed, using one with predictable pharmacokinetics and pharmacodynamics is preferred to minimize unintentional overdose risk. In particular, unique characteristics of methadone and of transdermal fentanyl make safe prescribing of these medications for pain especially challenging. Methadone should not be the first choice for an ER/LA opioid. ***Only 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.*** A clinical practice guideline regarding methadone prescribing for pain has been published previously (Chou et al., 2014). ***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.***

4. **When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest dosage to achieve expected effects. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage,**

should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients (recommendation category: A, evidence type: 3).

Implementation considerations:

- *When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest dosage to achieve expected effects.*
- *For patients not already taking opioids, the lowest dose to achieve expected effects can be determined using product labeling as a starting point with calibration as needed based on the severity of pain and on other clinical factors such as renal or hepatic insufficiency (see Recommendation 8).*
- *The lowest starting dose for opioid-naïve patients is often equivalent to a single dose of approximately 5 to 10 MME or a daily dosage of 20-30 MME/day. A listing of common opioid medications and their dosage in MME equivalents is provided (Table).*
- *Risks of opioid use, including risk for overdose and overdose death, increase continuously with dosage, and there is no single dosage threshold below which risks are eliminated.*
- *If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage and should generally avoid dosage increases when possible.*
- *Many patients do not experience benefit in pain or function from increasing opioid dosages to ≥50 MME/day but are exposed to progressive increases in risk as dosage increases. Therefore, before increasing total opioid dosage to ≥50 MME/day, clinicians should pause and carefully reassess evidence of individual benefits and risks. If a decision is made to increase dosage, clinicians should use caution and increase dosage by the smallest practical amount.*
- *Additional dosage increases beyond 50 MME/day are progressively more likely to yield diminishing returns in benefits relative to risks to patients as dosage increases further. Clinicians should carefully evaluate a decision to further increase dosage based on individualized assessment of benefits and risks and weighing factors such as diagnosis, incremental benefits for pain and function relative to risks with previous dosage increases, other treatments and effectiveness, and patient values and preferences.*
- *The recommendations related to opioid dosages are not intended to be used as an inflexible, rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient decision making. Further, these recommendations apply specifically to starting opioids or to increasing opioid dosages, and a different set of benefits and risks applies to reducing opioid dosages (see Recommendation 5).*

Supporting Rationale

Benefits of high-dose opioids for pain are not well established. Few trials evaluated opioid dosages of (≥90 MME/day) (Chou et al., April 2020). Opioid dosages of 50 to 90 MME/day were associated with a minimally greater (below the threshold for small) improvement in mean pain intensity compared with doses less than 50 MME/day (mean difference -0.26, 95% CI -0.57 to -0.02); there was no difference in mean improvement in function (Chou et al., April 2020). Analyses of placebo-controlled trials also found some evidence of a plateauing effect at 50 mg or greater MME/day (Chou et al., April 2020). One trial of more liberal dose escalation compared with maintenance of current dosage found no difference in outcomes related to pain or function (Chou et al., April 2020).

At the same time, risks for serious harms related to opioid therapy, including opioid misuse, overdose, and death, increase at higher opioid dosage, without a single point below which there is no risk (Coyle et al., 2018). One cohort study from the clinical evidence reviews found higher dosages of opioids were associated with increased risk of all-cause mortality; one cohort study found modest associations between higher dose of long-term opioid and increased risk of falls and major trauma; one case-control study found opioid doses higher than 20 MME/day were associated with increased odds of road trauma injury when the analysis was restricted to drivers, with no dose-dependent association at doses higher than 20 MME/day; and cohort studies found association between higher opioid dose and risk of various endocrinological adverse events (Chou et al., April 2020). Patients on higher doses reported reliance on opioids despite ambivalence about their benefits (Chou et al., April 2020).

Four observational studies identified in the clinical evidence reviews consistently found an association between higher doses of long-term opioids and risk of overdose or overdose mortality (Chou et al., April 2020). Opioid dosages for chronic pain of 50–<100 MME/day in observational studies have been associated with increased risks for opioid overdose by factors of 1.9 to 4.6 compared with dosages of 1–<20 MME/day, and dosages ≥100 MME/day with increased risks of overdose 2.0–8.9 times the risk at 1–<20 MME/day, after adjusting for confounders based on demographics, comorbidities, concomitant

medications, and other factors (Bohnert et al., 2011; Dunn et al., 2010; Gomes, Mamdani, Dhalla, Paterson, & Juurlink, 2011). When prescribed for acute pain, similar associations have been found, with dosages of 50–<100 MME/day associated with 4.73 times and dosages ≥100 MME/day associated with 6.64 times the risk for opioid overdose compared with dosages of 1–<20 MME/day (Bohnert et al., 2011). The MME cut points in these studies (e.g., 20 MME, 50 MME, 100 MME) were selected by the authors for research purposes, and while their findings are consistent with progressive increases in overdose risk being associated with increases in prescribed opioid dosages, they do not demonstrate a specific dosage threshold below which opioids are never associated with overdose. In a national sample of Veterans Health Administration patients with chronic pain who were prescribed opioids, mean prescribed opioid dosage among patients who died from opioid overdose was 98 MME (median 60 MME) compared with mean prescribed opioid dosage of 48 MME (median 25 MME) among patients not experiencing fatal overdose (Bohnert, Logan, Ganoczy, & Dowell, 2016). A narrative review conducted by FDA staff concluded that although there is not a single dosage threshold below which overdose risk is eliminated (Coyle et al., 2018), the studies included in the review show an increasing risk of serious adverse health outcomes, including misuse, overdose, and death associated with increasing opioid dose. Note that these studies examined dose-response risk of overdose for full-agonist opioids and not for partial agonist opioids such as buprenorphine, which is unlikely to have the same continuous association between dosage and overdose risk because respiratory depressant effects of buprenorphine reach a plateau (Dahan et al., 2006).

Several experts expressed concern that including specific dosage thresholds in a main recommendation statement would emphasize them as “authoritative” absolutes and would lead to non-collaborative tapers or other potentially harmful consequences. In addition, experts noted the lack of a single standard formula for calculating MMEs (Dasgupta et al., 2021). However, experts agreed there is a need for thresholds as benchmarks and suggested instead including them in the supporting text

following the main recommendation statement. Experts also agreed with separating recommendations on dosage into a recommendation applying to patients starting opioids and patients already receiving opioids at higher dosages.

When opioids are used for acute, subacute, or chronic pain, clinicians should start opioids at the lowest possible effective dosage. ***For patients not already taking opioids, the lowest dose to achieve expected effects can be determined using product labeling as a starting point with calibration as needed based on the severity of pain and on other clinical factors such as renal or hepatic insufficiency (see Recommendation 8). The lowest starting dosage for opioid-naïve patients is often equivalent to a single dose of approximately 5 to 10 MME or a daily dosage of 20-30 MME/day.*** A listing of common opioid medications and their dosage in MME equivalents is provided (Table). For example, a label for hydrocodone bitartrate (5mg) and acetaminophen (SpecGx LLC, 2021) (300mg) states that "the usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets." Clinicians should use additional caution when initiating opioids for patients aged ≥65 years and for patients with renal or hepatic insufficiency because of a potentially smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (see Recommendation 8). Formulations with lower opioid doses (e.g., hydrocodone bitartrate 2.5 mg with acetaminophen 325 mg) are available and can facilitate dosing when additional caution is needed. Product labeling regarding tolerance includes guidance for patients already taking opioids. In addition to opioids, clinicians should consider cumulative dosages of other medications, such as acetaminophen, that are combined with opioids in many formulations and for which decreased clearance of medications might result in accumulation of medications to toxic levels. Acetaminophen can be hepatotoxic at dosages of >3–4 grams/day and at lower dosages in patients with chronic alcohol use or liver disease (American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009).

Clinicians should generally avoid unnecessary dosage increases, use caution when increasing opioid dosages, and increase dosage by the smallest practical amount because overdose risk increases with increases in opioid dosage. Although there is limited evidence to recommend specific intervals for dosage titration, rapid dosage increases put patients at greater risk for sedation, respiratory depression, and overdose. For opioid-naïve outpatients with acute pain treated with an opioid for a few days or less, dosage increases are usually unnecessary and should not be attempted without close monitoring, given the risks of respiratory depression. In the context of long-term opioid use, when dosage is increased, clinicians should re-evaluate patients after increasing dosage for changes in pain, function, and risk for harm (see Recommendation 7).

Before increasing total opioid dosage to ≥50 MME/day, clinicians should pause, given that dosage increases to more than 50 MME/day are unlikely to provide significantly improved pain control for most patients while overdose risk increases with dosage, and carefully reassess evidence of individual benefits and risks. If a patient's opioid dosage for all sources of opioids combined reaches or exceeds 50 MME/day, clinicians should implement additional precautions, including increased frequency of follow-up (see Recommendation 7) and offer naloxone and overdose prevention education to both patients and the patients' household members (see Recommendation 8).

Additional dosage increases beyond 50 MME/day are progressively more likely to yield diminishing returns in benefits relative to risks to patients, and clinicians should carefully evaluate a decision to increase dosage based on individualized assessment of benefits and risks and weighing factors such as diagnosis, incremental benefits for pain and function relative to risks with previous dosage increases, other treatments and effectiveness, and patient values and preferences.

Some states require clinicians to implement clinical protocols at specific dosage levels. For example, before increasing long-term opioid therapy dosage to >120 MME/day, clinicians in Washington state must obtain consultation from a pain specialist who agrees that this is indicated and appropriate

(State of Washington Department of Health, 2019). Clinicians should be aware of rules related to MME thresholds and associated clinical protocols established by their states.

5. **For patients already receiving higher opioid dosages, clinicians should carefully weigh benefits and risks and exercise care when reducing or continuing opioid dosage. If risks outweigh benefits of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to lower dosages or, if warranted based on the individual clinical circumstances of the patient, to appropriately taper and discontinue opioids. Unless there are indications of a life-threatening issue, such as warning signs of impending overdose, e.g., confusion, sedation, or slurred speech, opioid therapy should not be discontinued abruptly, and clinicians should not abruptly or rapidly reduce opioid dosages from higher dosages (recommendation category: B, evidence type: 4).**

Implementation considerations:

- *Clinicians should consider tapering to a reduced opioid dosage, or tapering and discontinuing opioid therapy, and discuss these approaches with patients prior to initiating changes, when risks outweigh benefits (potentially including avoiding risks of tapering) of continued opioid therapy.*
- *Patient agreement and interest in tapering is likely to be a key component of successful tapers.*
- *For patients agreeing to taper to lower opioid dosages as well as for those remaining on higher opioid dosages, clinicians should establish goals with the patient for continued opioid therapy (see Recommendations 2 and 7) and maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).*
- *Clinicians should collaborate with the patient on the tapering plan, including patients in decisions such as how quickly tapering will occur and when pauses in the taper may be warranted.*
- *Clinicians should follow up frequently (at least monthly) with patients engaging in opioid tapering.*
- *When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should be used.*

- *Tapers can be completed over several months to years depending on the opioid dosage and should be individualized based on patient goals and concerns. Longer durations of previous opioid therapy might require longer tapers.*

- *Tapers of 10% per month or slower are likely to be better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations (e.g., for a year or longer).*

- *Significant opioid withdrawal symptoms can signal the need to further slow the taper rate.*

- *At times, tapers might have to be paused and restarted again when the patient is ready and might have to be slowed once patients reach low dosages.*

- *Tapers should not be reversed without careful assessment of benefits and risks of increasing opioid dosage or without maximizing nonopioid treatments for pain and addressing behavioral distress.*

- *Once the smallest available dose is reached, the interval between doses can be extended.*

- *Goals of the taper may vary—some patients might achieve discontinuation; others might attain a reduced dosage. If the clinician has determined with the patient that the ultimate goal of tapering is discontinuing opioids, opioids may be stopped when taken less frequently than once a day.*

- *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.*

- *Clinicians should advise patients that there is an increased risk for overdose on abrupt return to a previously prescribed higher dose, caution that it takes as little as a week to lose tolerance, provide opioid overdose education, and offer naloxone.*

- *Clinicians should remain alert to signs of anxiety, depression, and opioid misuse or opioid use disorder (see Recommendations 8 and 12) that might be revealed by an opioid taper and provide treatment or arrange for management of these co-morbidities.*

- *Clinicians should closely monitor patients who are unable to taper and who continue on high-dose or otherwise high-risk opioid regimens (e.g., opioids prescribed concurrently with benzodiazepines) and should work with patients to mitigate overdose risk (e.g., by providing overdose education and naloxone—see Recommendation 8).*

- *Clinicians can use periodic and strategic motivational questions and statements to encourage movement toward appropriate therapeutic changes and functional goals.*

- *Clinicians have a responsibility to provide or arrange for coordinated management of patients' pain and opioid-related problems, including opioid use disorder.* ***Clinicians should not abandon patients.***

- *Payers, health systems, and state medical boards should not use this clinical practice guideline to set rigid standards related to dose or duration of opioid therapy, and should ensure that policies based on cautionary dosage thresholds do not result in rapid tapers or abrupt discontinuation of opioids, and that policies do not penalize clinicians for accepting new patients who are using prescribed opioids for chronic pain, including those receiving high doses of opioids.*

- *While Recommendation 5 specifically refers to patients using long-term, high-dose opioid therapy for subacute or chronic pain, many of the principles in these implementation considerations and supporting rationale, including communication with patients, pain management and behavioral support, and slower taper rates, are also relevant when discontinuing opioids in patients receiving shorter durations and/or lower-dosages (see also Recommendations 6 and 7).*

Supporting Rationale

Patients receiving long-term, high dose opioid therapy for chronic pain are at increased risk for adverse events including overdose mortality (Bohnert et al., 2011; Dunn et al., 2010; Gomes et al., 2011; K. S. Gordon et al., 2020; Kaplovitch et al., 2015). However, discontinuation of long-term, high dose opioid therapy has been associated with adverse events including mental health crisis, overdose events, and overdose mortality (Agnoli et al., 2021; K. S. Gordon et al., 2020; James et al., 2019; Mark & Parish, 2019). One study found that while sustained opioid therapy discontinuation (defined by the authors as opioid discontinuation for at least 3 months) was associated with an approximate 50% reduction in risk of overdose, dose variability was a risk factor for opioid overdose (Glanz, Binswanger, Shetterly, Narwaney, & Xu, 2019). Another study found that both starting and stopping opioids were associated with overdose or suicide risk; risk associated with stopping increased the longer patients had received opioids before stopping. Death rates for overdose or suicide increased immediately after starting or stopping treatment with opioids, with the incidence decreasing over about three to twelve months (E. M. Oliva et al., 2020). In particular, discontinuation of opioids over short time periods has been associated with greater risks. FDA has advised that risks of rapid tapering or sudden discontinuation of opioids in physically dependent patients include acute withdrawal symptoms, exacerbation of pain, serious psychological distress, and thoughts of suicide (U.S. Food and Drug Administration, 2019c). One

observational study found that among adults prescribed stable higher opioid dosages (mean ≥50 MME/day) long-term, increasing maximum monthly dose reduction velocity by 10% was associated with an adjusted incidence rate ratio of 1.09 for overdose (95% CI, 1.07-1.11) and of 1.18 for mental health crisis (95% CI, 1.14-1.21) (Agnoli et al., 2021). Another study of patients on long-term, high-dose (≥120 MME/day) opioid therapy found that each additional week of tapering time before opioid discontinuation was associated with a 7% relative reduction in the risk of opioid-related emergency department visits or hospitalizations (Mark & Parish, 2019). The clinical evidence reviews did not find studies comparing different rates of opioid tapering, but a taper support intervention (psychiatric consultation, opioid dosage tapering, and 18 weekly meetings with a physician assistant to explore motivation for tapering and learn pain self-management skills) was associated with better functional outcomes (specifically improvement in pain interference) compared to usual care, with effects persisting at 34-week follow-up (Chou et al., April 2020). A systematic review (Frank et al., 2017) found that among studies rated as "good" or "fair" quality, when opioids were tapered following discussion with patients who agreed to taper, opioid dose reduction was associated with improved pain, function, and quality of life. These results suggest that involving patients in decisions regarding continuation or discontinuation of opioid analgesics, as well as practices including behavioral support, integration of nonpharmacologic pain management, and slower tapers, may improve outcomes.

Experts appreciated the complexity of managing patients already receiving higher dosages of opioids long-term. While some experts felt there should be more consideration of obtaining informed consent prior to tapering opioids, others believed that informed discussion is more appropriate than informed consent when considering tapering opioids given clinicians' overriding responsibility to avoid providing treatment that harms patients. Some experts were concerned that over-emphasizing risks of tapering could increase harm from continued high-dosage opioid use.

Determining whether, when, and how to taper opioids

The benefits and the risks of opioid therapy change over time and should be re-evaluated periodically (see Recommendations 6 and 7). Opioid therapy should be limited to circumstances where benefits of therapy outweigh risks. Because tapering opioids can be harmful in some circumstances, benefits of continuing opioids in patients who have already received them long term might include avoiding risks of tapering and discontinuing opioids. In situations where benefits and risks of continuing opioids are considered to be close, shared decision-making with patients is particularly important. ***Unless there is a life-threatening issue, such as imminent overdose, the benefits of rapidly tapering or abruptly discontinuing opioids are unlikely to outweigh the significant risks of these practices*** (Mark & Parish, 2019; U.S. Department of Health and Human Services, 2019a). However, following slow, voluntary reduction of long-term opioid dosages, many patients report improvements in function, quality of life, anxiety, and mood without worsening pain or with decreased pain levels (Frank et al., 2017). Clinicians and patients should consider whether opioids continue to meet treatment goals, whether opioids are exposing the patient to an increased risk for serious adverse events or opioid use disorder, and whether benefits continue to outweigh risks of opioids. Clinicians should not insist on opioid tapering or discontinuation when opioid use may be warranted (i.e., when benefits of opioids outweigh risks) (Kroenke et al., 2019; U.S. Department of Health and Human Services, 2019a). 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. For pregnant people with opioid use disorder, medications for opioid use disorder are preferred over withdrawal management (i.e., discontinuation of opioids through either short- or medium-term tapering) (American Society of Addiction Medicine, 2015; Ecker et al., 2019; Substance Abuse and Mental Health Services Administration, 2018b).

Some patients using more than one respiratory depressant (e.g., benzodiazepines and opioids) might require tapering one or more medications to reduce risk for respiratory depression. Tapering decisions and plans should be coordinated with prescribers of all respiratory depressant medications (see Recommendation 11). If benzodiazepines are tapered, they should be tapered gradually due to risks of benzodiazepine withdrawal (anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death (Haque, Watson, & Bryant, 1990; Lann & Molina, 2009)). Patients who are not actually taking opioids (such as patients who are diverting all opioids they obtain) do not require tapers.

Consistent with the HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics (U.S. Department of Health and Human Services, 2019a), clinicians should consider tapering to a reduced opioid dosage, or tapering and discontinuing opioid therapy, and discuss with these approaches with patients prior to initiating changes when

- The patient requests dosage reduction or discontinuation
- Pain improves and might indicate resolution of an underlying cause
- When opioid therapy has not meaningfully reduced pain or improved function
- The patient has been treated with opioids for a prolonged period (e.g., years), and current benefit-risk balance is unclear (e.g., decreased positive effects due to tolerance, symptoms such as reduced focus or memory that might be due to opioids)
- The patient is receiving higher opioid doses without evidence of benefit from the higher dose
- The patient experiences side effects that diminish quality of life or impair function
- There is current evidence of opioid misuse
- The patient experiences an overdose or other serious event (e.g., an event leading to hospitalization or injury) or has warning signs for an impending event such as confusion, sedation, or slurred speech

- The patient is receiving medications (e.g., benzodiazepines) or has medical conditions (e.g., lung disease, sleep apnea, liver disease, kidney disease, fall risk, advanced age) that increase risk for adverse outcomes

Clinicians should review benefits and risks of continued high-dose opioid therapy with patients. Established patients already taking high dosages of opioids, as well as patients transferring from other clinicians, might consider the possibility of opioid dosage reduction to be substantially anxiety-provoking, and tapering opioids can be especially challenging after years on high dosages because of physical and psychological dependence. However, patients should be offered the opportunity to re-evaluate their continued use of opioids at high dosages. Clinicians should empathically review benefits and risks of continued high-dosage opioid therapy and should offer to work collaboratively with the patient to taper opioids to safer dosages.

Whenever possible, clinicians should collaborate with patients in making decisions about whether and how to taper opioids and share decision-making with patients. Whether the goal of the taper is stopping opioids or reducing opioids to a point where benefits outweigh risks depends on the individual patient's circumstances and individualized assessment of benefits and risks, informed by open discussion between the patient and clinician. Tapering is more likely to be successful when patients collaborate in the taper (Dowell & Haegerich, 2017). Clinicians should review risks and benefits of the current therapy with the patient and decide if tapering is appropriate based on individual circumstances. Clinicians can discuss with patients their perceptions of risks, benefits, and adverse effects of continued opioid therapy, include patient concerns in taper planning, and include patients in decisions such as which medication will be decreased first and how quickly tapering will occur. If the current opioid regimen does not put the patient at imminent risk, tapering does not need to occur immediately, and clinicians can take time to obtain patient buy-in (Dowell & Haegerich, 2017). For patients who agree to

taper opioids to lower dosages, clinicians should collaborate with the patient on a tapering plan, including patients in decisions, such as which medication will be decreased first (e.g., in patients prescribed more than one opioid) and how quickly tapering will occur.

Advice to patients prior to tapering

Patients should be advised that overall, following voluntary reduction of long-term opioid dosages, most patients report stable or improved function, anxiety, and mood without worsening pain or even with decreased pain levels (Berna, Kulich, & Rathmell, 2015; Darnall et al., 2018; Frank et al., 2017; Goesling et al., 2019; Kroenke et al., 2019; Sullivan et al., 2017). Other patients report insomnia, anxiety, depression, and increased pain, particularly in the short term (Berna et al., 2015; Goesling et al., 2019; Kroenke et al., 2019; Manhapra, Arias, & Ballantyne, 2018; Sturgeon, Sullivan, Parker-Shames, Tauben, & Coelho, 2020). Increased pain may be related to hyperalgesia or opioid withdrawal and can be prolonged in some patients (Manhapra et al., 2018). It can be helpful to counsel patients that worsening of pain is a frequent symptom of opioid withdrawal that tends to diminish over time (U.S. Department of Health and Human Services, 2019a). Clinicians should advise patients that there is an increased risk for overdose on abrupt return to a previously prescribed higher dose, caution that it takes as little as a week to lose tolerance, and warn that there is a risk of overdose if they return to their original dose (U.S. Department of Veterans Affairs and Department of Defense, 2017). Clinicians should provide opioid overdose education and offer naloxone.

Pain management during tapering

Clinicians should commit to working with patients to improve function and decrease pain, whether or not opioids are tapered. Nonopioid treatments should be integrated into patients' pain management plans based on an individualized assessment of benefits and risks considering the patient's diagnosis, circumstances, and unique needs (see Recommendation 2). Integrating behavioral and nonopioid pain therapies before and during a taper can help manage pain (Frank et al., 2017) and

strengthen the therapeutic relationship. For patients agreeing to taper to lower opioid dosages as well as for those remaining on higher opioid dosages, clinicians should establish goals with the patient for continued opioid therapy (see Recommendations 2 and 7) and maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).

Behavioral health support during tapering

Integrating behavioral and nonopioid pain therapies and treatment for comorbid mental health conditions before and during a taper can help manage pain (Frank et al., 2017), strengthen the therapeutic relationship, and improve the likelihood of positive tapering outcomes (Sullivan et al., 2017). Mental health co-morbidities including depression and anxiety are common in patients with painful conditions, especially in patients receiving long-term opioid therapy (Sullivan, 2018). Depressive symptoms predict taper dropout (Berna et al., 2015; Darnall et al., 2018). Primary care clinicians should collaborate with mental health specialists and with other specialty clinicians as needed to optimize nonopioid pain management (see Recommendation 2), as well as psychosocial support for anxiety related to the taper. Clinicians should consider arranging for consultation with a behavioral health specialist before initiating a taper in patients with serious mental illness, who are at high suicide risk, or with suicidal ideation (U.S. Department of Health and Human Services, 2019a). Clinicians should remain alert to signs of anxiety, depression, and opioid misuse or opioid use disorder (see Recommendations 8 and 12) that might be revealed by an opioid taper and provide treatment or arrange for management of these co-morbidities. Successful tapering studies have used at least weekly follow-up (Frank et al., 2017), and clinicians should follow up frequently (at least monthly) with patients engaging in opioid tapering. Clinicians can acknowledge patient fears about tapering (Veterans Health Administration PBM Academic Detailing Service, 2016), ask how they can support the patient (Veterans Health Administration PBM Academic Detailing Service, 2016), and make sure patients receive appropriate and accessible psychosocial support (Sullivan et al., 2017; U.S. Department of Veterans Affairs and

Department of Defense, 2017). Many patients fear stigma, withdrawal symptoms, pain, and/or abandonment (Henry et al., 2019), and it can be helpful to tell patients what to expect (e.g., the rate will be kept slow to minimize withdrawal symptoms; pain may worsen at first but usually improves over time) and that the clinician will support them through the process.

Tapering rate

Evidence to support specific tapering rates is limited. The rate of tapering should be individualized based on the clinical situation of the patient. When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should be used. Tapers can be completed over several months to years depending on the opioid dosage and should be individualized based on patient goals and concerns. Longer durations of previous opioid therapy might require longer tapers. Evidence on optimal taper rate is emerging. ***Tapers of approximately 10% per month or slower are likely to be better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations (e.g., for a year or longer).*** A decrease of 10% of the original dose per week or slower (until approximately 30% of the original dose is reached, followed by a weekly decrease of approximately 10% of the remaining dose) is unlikely to trigger withdrawal (Berna et al., 2015) and can be successful for some patients, particularly after opioid use for weeks to months rather than years. Significant opioid withdrawal symptoms can signal the need to further slow the taper rate. At times, tapers might have to be paused and restarted again when the patient is ready and might have to be slowed once patients reach low dosages to allow gradual accommodation to lower opioid dosages and development of new skills for management of pain and emotional distress. Tapers should not be reversed without careful assessment of benefits and risks of increasing opioid dosage or without maximizing nonopioid treatments for pain and addressing behavioral distress (Rich et al., 2020). Once the smallest available dose is reached, the interval between

doses can be extended. If the clinician has determined with the patient that the goal is discontinuing opioids, opioids may be stopped when taken less frequently than once a day.

More rapid tapers might be needed for patient safety under certain circumstances (e.g., for patients who have experienced overdose on their current dosage). However, ***unless there are indications of a life-threatening issue, such as warning signs of impending overdose, opioid therapy should not be discontinued abruptly, and clinicians should not abruptly reduce opioid dosages from higher dosages.*** When opioids have been prescribed continuously for longer than a few days, sudden discontinuation may precipitate significant opioid withdrawal (Mark & Parish, 2019). Rapid tapering or sudden discontinuation of opioids in physically dependent patients can also increase risks of psychological distress and opioid-related emergency department visits and hospitalizations (Mark & Parish, 2019; U.S. Food and Drug Administration, 2019c). Ultrarapid detoxification under anesthesia is associated with substantial risks, including death, and should not be used (Berlin et al., 2013).

Management of opioid withdrawal during tapering

The first approach to withdrawal symptoms and signs should generally be consideration of slowing or pausing the taper rate. If needed, short-term oral medications might also help manage withdrawal symptoms (Veterans Health Administration PBM Academic Detailing Service, 2016). These include alpha-2 agonists for the management of autonomic signs and symptoms (e.g., sweating, tachycardia). Alpha-2 agonists clonidine and lofexidine are more effective than placebo in reducing severity of withdrawal (Gowing, Farrell, Ali, & White, 2016) from heroin or methadone in the context of abrupt (not gradual) discontinuation. There is not similar research in patients tapering from long-term opioid treatment for pain (Berna et al., 2015), but the alpha-2 agonist tizanidine has been used to help taper patients from long-term, high-dose opioids for chronic pain (Sturgeon et al., 2020). Other medications addressing specific symptoms (NSAIDs, acetaminophen, or topical menthol/methyl salicylate for muscle aches; trazodone for sleep disturbance; prochlorperazine, promethazine, or

ondansetron for nausea; dicyclomine for abdominal cramping; and loperamide or bismuth subsalicylate for diarrhea) have also been used (Veterans Health Administration PBM Academic Detailing Service, 2016).

Tapering when patients have opioid use disorder

Some patients with unanticipated challenges to tapering, such as inability to make progress in tapering despite opioid-related harm, might have undiagnosed opioid use disorder. Therefore, patients experiencing such challenges should be assessed for opioid use disorder using *Diagnostic and Statistical Manual of Mental Disorders* (*Fifth Edition*) criteria and if criteria for opioid use disorder are met, offered medication treatment (see Recommendation 12) and naloxone for opioid overdose reversal (see Recommendation 8).

Other challenges to tapering

Emerging evidence suggests that patients for whom risks of continued high-dose opioid use outweigh benefits but who are unable to taper and who do not meet criteria for opioid use disorder might benefit from transition to buprenorphine (Chou, Ballantyne, & Lembke, 2019; Fishman & Kim, 2018; U.S. Department of Health and Human Services, 2019a). Buprenorphine is an opioid partial agonist that can treat pain as well as opioid use disorder (Pade, Cardon, Hoffman, & Geppert, 2012), and has other properties that may be helpful (U.S. Department of Veterans Affairs and Department of Defense, 2017), including less respiratory depression (Dahan et al., 2006) and overdose risk than other opioids (Chou et al., 2019). While overdose is less likely with buprenorphine than with full agonist opioids, overdose is still possible, particularly if buprenorphine is taken concurrently with other respiratory depressants, such as full agonist opioids, benzodiazepines, or alcohol (Paone et al., 2015). A specialty clinic offering opioid tapering services for patients receiving high-dosage opioids (defined in this study as $\geq$90 MME/day) for chronic pain found that 44.6% of patients referred for opioid taper were

able to successfully taper to <90 MME/day, and an additional 18.8% who were unable to taper were able to successfully transition to sublingual buprenorphine (Sturgeon et al., 2020). Different buprenorphine products, available at different doses, are approved for the treatment of pain (e.g., Belbuca, Butrans) and for the treatment of opioid use disorder (e.g., Suboxone). While prescription of buprenorphine for treatment of opioid use disorder requires the clinician to have a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) (see Recommendation 12), prescription of buprenorphine for treatment of chronic pain does not require a waiver(Chou et al., 2019).

To avoid precipitating withdrawal, transitioning any patient taking full agonist opioids to buprenorphine requires careful timing of the initial buprenorphine dose (U.S. Department of Health and Human Services, 2019a) (see Recommendation 12 for application to patients with opioid use disorder). Patients should be in mild to moderate withdrawal from full agonist opioids before the first buprenorphine dose (U.S. Department of Health and Human Services, 2019a). To do this, it has been advised to wait at least 8 to 12 hours after the last dose of short-acting full agonist opioids and waiting longer following the last dose of long-acting full agonist opioids (e.g., at least 12-24 hours after the last dose of an ER/LA full-agonist opioid, longer for methadone) before the first dose of buprenorphine (Manhapra et al., 2018). As an alternative for patients not yet in opioid withdrawal, some authors have described low dose initiation of buprenorphine to allow for initiation of buprenorphine in patients currently receiving full agonist opioids for acute or chronic pain (Cohen et al., 2021). SAMHSA's Providers Clinical Support System (https://pcssnow.org/) offers training and technical assistance as well as mentors to assist clinicians who are unfamiliar with initiation of buprenorphine and have additional questions related to the diagnosis and treatment of opioid use disorder in particular. Because the duration of action for analgesia is shorter than the duration of action for suppression of opioid withdrawal and stabilization of opioid use disorder (Alford, Compton, & Samet, 2006), dosing

buprenorphine for pain is typically multiple times daily (e.g., 8mg sublingual tablet three times a day) rather than once a day dosing as done for the treatment of OUD (Manhapra et al., 2018; U.S. Department of Veterans Affairs and Department of Defense, 2017).

Continuing high-dosage opioids

Clinicians should closely monitor patients who are unable to taper and who continue on high-dose or otherwise high-risk opioid regimens (e.g., opioids prescribed concurrently with benzodiazepines) and should work with patients to mitigate overdose risk (e.g., by providing overdose education and naloxone—see Recommendation 8). Clinicians can use periodic and strategic motivational questions and statements to encourage movement toward appropriate therapeutic changes (Dowell & Haegerich, 2017). Increasing opioid dosage in patients already receiving high dosages is likely to be associated with diminishing returns for pain relief and increased risks for adverse effects and should be avoided.

Management of chronic pain with opioids can be challenging, as can management of opioid discontinuation (Dowell, Haegerich, et al., 2019). However, ***clinicians have a responsibility to provide or arrange for coordinated management of patients' pain and opioid-related challenges. Clinicians should not abandon patients. Payers and health systems should not use this clinical practice guideline to set rigid standards related to dose or duration of opioid therapy, should ensure that policies based on cautionary dosage thresholds do not result in rapid tapers or abrupt discontinuation of opioids.*** Care should be taken to ensure that policies do not penalize clinicians for accepting new patients who are receiving opioids for chronic pain. Patients prescribed opioids but unable to access ongoing care (Lagisetty et al., 2019) may be at risk for abrupt opioid discontinuation and may miss opportunities to receive life-saving interventions, including monitoring for and management of mental health and substance use co-morbidities.

Opioid duration and follow-up

6. When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids (recommendation category: A, evidence type: 4).

Implementation considerations:

- *Nontraumatic, nonsurgical acute pain can often be managed without opioids (see Recommendation 1).*
- *Opioids are sometimes needed for treatment of acute pain (see Recommendation 1). When the diagnosis and severity of acute pain warrant use of opioids, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. For many common causes of nontraumatic, nonsurgical pain, when opioids are needed, a few days or less are often sufficient, and shorter courses can minimize the need to taper opioids to prevent withdrawal symptoms at the end of a course of opioids. However, durations should be individualized based on the clinical circumstances of the specific patient.*
- *Clinicians should generally avoid prescribing additional opioids to patients "just in case" pain continues longer than expected.*
- *For postoperative pain related to major surgery, procedure-specific opioid prescribing recommendations are available with ranges for amounts of opioids needed (based on actual use and refills and on consensus).*
- *To minimize unintended impact on patients with an unexpectedly prolonged duration of severe acute pain, clinicians, practices, and health systems should have mechanisms in place to provide timely re-evaluation for 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. In particular, clinicians, practices, and health systems should ensure all patients can access and afford additional evaluation and treatment, as needed, to minimize disparities across patients based on access to and affordability of care and refills.*
- *Longer durations of opioid therapy are more likely to be needed when the mechanism of injury is expected to result in prolonged severe pain (e.g., severe traumatic injuries).*
- *Patients should be evaluated at least every 2 weeks if they continue to receive opioids for acute pain.*
- *If opioids are continued for a month or longer, clinicians should refer to recommendations on subacute and chronic pain for follow-up (Recommendation 7) and tapering (Recommendation 5).*
- *If patients already receiving long-term opioids require additional opioids for superimposed severe acute pain (e.g., major surgery), opioids should be continued only for the duration of pain severe enough to require additional opioids, returning to the patient's baseline opioid dosage as soon as possible, including a taper to baseline dosage if additional opioids were used around the clock for more than a few days.*
- *If opioids are prescribed continuously (around the clock) for more than a few days for acute pain, clinicians should prescribe a taper to minimize withdrawal symptoms on discontinuation of opioids.*

- *Taper durations might need to be adjusted depending on the duration of the initial opioid prescription (see supporting rationale for this recommendation for additional details).*
- *Tapering plans should be discussed with the patient prior to hospital discharge and with clinicians coordinating the patient's care as an outpatient. For tapering considerations when patients have taken opioids continuously for longer than one month, see Recommendation 5.*

Supporting Rationale

Data suggest that for many patients presenting with common types of acute pain in primary care or emergency department settings, pain improves within days. Analysis of nationwide U.S. commercial insurance claims in 2014 found median durations of initial opioid analgesic prescriptions for acute pain indications in primary care settings were 4–7 days (Mundkur et al., 2019), suggesting that in most cases, clinicians considered an initial opioid prescription of 4 to 7 days' duration sufficient. Some patients (17.8%, ranging from 11.7% to 30.0% depending on the acute pain condition) obtained at least one refill within 30 days after their initial opioid prescription, suggesting that while for most patients, these durations might have been sufficient or more than necessary, there is likely to be variation across diagnoses and among patients in time to recovery. In an older study of the course of acute low back pain (not associated with malignancies, infections, spondyloarthropathies, fractures, or neurological signs) in a primary care setting, there was a large decrease in pain until the fourth day after treatment with paracetamol, with smaller decreases thereafter (Coste, Delecoeuillerie, de Lara, LeParc, & Paolaggi, 1994). A more recent single-center survey of patients prescribed opioids for acute pain on emergency department discharge (McCarthy et al., 2021) found that patients taking opioids continued them for a median of 4 days (interquartile range [IQR] 2-7 days), including on the day of discharge, with variation across patients and diagnoses. Median numbers of days that patients continued taking prescribed opioids were 6 (IQR 4-8) for back pain and for fractures, 2 (IQR 1-5) for renal colic, 5.5 (IQR 4-7) for musculoskeletal injury, and 3 (IQR 2-6) for other diagnoses. Most patients (92.5%) reported having leftover pills, with 52.2% of pills unused overall. A Canadian study following patients for 14 days after

discharge from the emergency department with opioid prescriptions for acute pain (Daoust et al., 2018) similarly found most (68%) total prescribed opioids were unused, and that the quantity of morphine 5mg tablets to prescribe in order to adequately supply 80% of the patients with the amount of opioids they actually used was 20 tablets for musculoskeletal pain, 30 for fracture, 15 for renal colic or abdominal pain, and 20 for other pain conditions.

Multiple studies since 2017 have found that many patients do not use all prescribed opioids after surgery and that prescribing a lower quantity of opioids postoperatively is associated with less opioid use without increases in pain score or in requests for refills of pain medication, and without significant reductions in satisfaction with pain management (Hill et al., 2017; Hill, Stucke, McMahon, et al., 2018; Howard et al., 2018). One study found that, following 5 common surgical procedures, median opioid consumption was three 5mg oxycodone pills or less, and that following consensus recommendations intended to reduce unnecessary postoperative opioid prescribing published in 2018 and 2019 would still result in 47% to 56% of pills prescribed remaining unused (K. A. Robinson et al., 2020). There is also evidence of variation in opioid needs across patients undergoing the same procedures based on individual factors including pain at discharge and prior opioid use (Mallama et al., 2021). One study found that while a majority of patients used no or few (less than a total of 50 MME during their entire postoperative course) opioids, some patients required opioids for up to 15 days after surgery (Thiels et al., 2018).

The clinical evidence reviews found observational evidence that opioid use for acute pain is associated with long-term opioid use, and that a greater amount of early opioid exposure is associated with greater likelihood of long-term use, noting recent evidence for a dose and duration-response relationship (Brat et al., 2018; Brummett et al., 2017; Mundkur et al., 2019; National Conference of State Legislatures, June 30, 2019.; Reznikoff, 2018; Shah et al., 2017). Opioids prescribed for surgery and other acute pain conditions that go unused (Bartels et al., 2016; Bicket, Long, Pronovost, Alexander, & Wu,

2017; Mallama et al., 2021; Neuman, Bateman, & Wunsch, 2019) are a potential source for misuse and diversion. In addition, sudden discontinuation of opioids used continuously for longer than a few days may result in significant opioid withdrawal (Mark & Parish, 2019). Therefore, limiting duration of opioids prescribed can minimize the need for a taper to prevent distressing or unpleasant withdrawal symptoms.

Many common causes of nonsurgical, nontraumatic acute pain can often be managed without opioids (see Recommendation 1). When the diagnosis and severity of acute pain warrant the use of opioids, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. A few days or less are often sufficient when opioids are needed for many common causes of nonsurgical acute pain and limiting the duration of opioid therapy can minimize the need to taper to prevent withdrawal symptoms at the end of the course of opioids as well as limiting unused opioids. Certain circumstances (e.g., severe traumatic injuries) might require use of opioids for durations greater than 7 days. Durations should be individualized based on the clinical circumstances of the specific patient.

When patients are discharged from the hospital following surgery, the course and dosage of any opioid medications given during hospitalization and prior to discharge can help predict ongoing pain management needs (Hill, Stucke, Billmeier, et al., 2018; Joo et al., 2020; Tamboli et al., 2020). For postoperative pain, procedure-specific opioid prescribing recommendations are available with ranges for amounts of opioids needed (based on actual use and refills and on consensus) (Michigan Opioid Prescribing Engagement Network, 2020; Overton et al., 2018) (Thiels et al., 2018).

Clinicians should generally not prescribe additional opioids to patients “just in case” pain continues longer than expected. However, in the event that pain continues longer than expected, it might be challenging for some patients to successfully navigate the healthcare system (e.g., clinician and pharmacy contact, transportation, need for assistance) to obtain additional medication as needed,

leading to potential disparities in treatment. Clinicians, practices, and health systems should have mechanisms in place to provide timely re-evaluation for 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 pain management accordingly. In particular, clinicians, practices, and health systems should ensure all patients can access and afford additional evaluation and treatment as needed to minimize disparities across patients based on access to and affordability of care and refills.

Patients should be evaluated at least every 2 weeks if they continue to receive opioids for acute pain, and if opioids are continued for a month or longer, clinicians should refer to recommendations on subacute and chronic pain for follow-up (Recommendation 7) and tapering (Recommendation 5). If patients already receiving long-term opioids require additional opioids for superimposed severe acute pain (e.g., major surgery), opioids should be continued only for the duration of pain severe enough to require additional opioids, returning to the patient's baseline opioid dosage as soon as possible, including a taper to baseline dosage if additional opioids were used around the clock for more than a few days.

If opioids are prescribed continuously (around the clock) for more than a few days for acute pain, clinicians should prescribe a taper to minimize withdrawal symptoms on discontinuation of opioids. Taper durations might need to be adjusted depending on the duration of the initial opioid prescription. For example, if opioids are used continuously for more than 3 days but for less than one week, clinicians can consider reducing the daily dosage to 50% for 2 days to ameliorate withdrawal when discontinuing opioids. When patients have taken opioids continuously for at least one week but less than one month, clinicians might consider a slower taper (e.g., reducing the daily dosage by approximately 20% every 2 days), a range consistent with tapering rates successfully used in studies of postoperative opioid prescribing (Joo et al., 2020; Tamboli et al., 2020). When patients are discharged from the hospital following surgery, opioid dosages needed during hospitalization and prior to discharge

can help predict tapering needs to prevent withdrawal (Hill, Stucke, Billmeier, et al., 2018; Joo et al., 2020; Tamboli et al., 2020). Tapering plans should be discussed with the patient prior to discharge and with clinicians coordinating the patient's care as an outpatient. For tapering considerations when patients have taken opioids continuously for longer than one month, see Recommendation 5.

7. **Clinicians should evaluate benefits and risks with patients within 1 to 4 weeks of starting opioid therapy for subacute or chronic pain or of dose escalation. Clinicians should evaluate benefits and risks of continued therapy with patients every 3 months or more frequently (recommendation category: A, evidence type: 4).**

Implementation considerations:

- *In addition to evaluating benefits and risks of opioids before starting opioid therapy (see Recommendation 2), clinicians should evaluate patients to assess benefits and risks of opioids within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation.*
- *Clinicians should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased, given increased risk for overdose within the first 2 weeks of treatment, or when total daily opioid dosage is ≥50 MME/day. (Note: Overdose risk is doubled across multiple studies for dosages of 50 to <100 MME/day relative to <20 MME/day - see Recommendation 4).*
- *Shorter follow-up intervals (within 3 days) should be strongly considered when starting or increasing the dosage of methadone, given the variable half-life of this drug (see Recommendation 3) and the potential for drug accumulation during initiation and during upward titration of dosage.*
- *An initial follow-up interval closer to 4 weeks can be considered when starting immediate-release opioids at a dosage <50 MME/day.*
- *Clinicians should regularly reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician but on long-term opioid therapy, at least every 3 months.*
- *Clinicians seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy (see Recommendation 2).*
- *Clinicians should re-evaluate patients who are at higher risk for opioid use disorder or overdose (e.g., patients with depression or other mental health conditions, a history of substance use disorder, a history of overdose, taking ≥50 MME/day, or taking other central nervous system depressants with opioids) more frequently than every 3 months.*

- *To minimize unintended impact on patients with challenges in accessing or affording follow-up visits, practices, and health systems should work to ensure all patients can access and afford follow-up evaluation.*

- *In practice contexts where virtual visits are part of standard care (e.g., in remote areas where distance or other context makes follow-up visits challenging), follow-up assessments that allow the clinician to communicate with and observe the patient through telehealth modalities may be conducted.*

- *At follow-up, clinicians should review patient perspectives and goals, determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function; whether the patient has experienced common or serious adverse events or early warning signs of serious adverse events or has signs of opioid use disorder.*

- *Clinicians should ensure that treatment for depression, anxiety, or other psychological co-morbidities is optimized.*

- *Clinicians should ask patients about their preferences for continuing opioids, given their effects on pain and function relative to any adverse effects experienced. If risks outweigh benefits of continued opioid therapy (e.g., if patients do not experience meaningful, sustained improvements in pain and function compared with prior to initiation of opioid therapy; if patients are taking higher-risk regimens [e.g., dosages ≥50 MME/day or opioids combined with benzodiazepines] without evidence of benefit; if patients believe benefits no longer outweigh risks; if patients request dosage reduction or discontinuation; or if patients experience overdose or other serious adverse events), clinicians should work with patients to reduce opioid dosage or to discontinue opioids when possible, using principles from Recommendation 5.*

- *Clinicians should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).*

Supporting Rationale

Although the clinical evidence reviews did not find studies evaluating the effectiveness of more frequent monitoring intervals (Chou et al., April 2020), they did identify an observational study (Edlund et al., 2014) finding risk for opioid use disorder was associated with continuing opioid therapy for 3 months or longer. In addition, the reviews identified a study finding that risk for overdose associated with ER/LA opioids might be particularly high during the first 2 weeks of treatment (Miller et al., 2015). Another study found the first 3 months after opioid initiation to be a higher risk period for opioid overdose (E. M. Oliva et al., 2020). Patients who do not have pain relief with opioids at 1 month are unlikely to experience pain relief with opioids at 6 months (Kalso, Simpson, Slappendel, Dejonckheere, &

Richarz, 2007). Although evidence is insufficient to determine at what point within the first 3 months of opioid therapy the risks for opioid use disorder increase, reassessment of pain and function within 1 month of initiating opioids provides an opportunity to modify the treatment plan to achieve pain treatment goals, minimize risks of long-term opioid use by tapering and discontinuing opioids among patients not receiving a clear benefit from these medications, and additional evaluation within the first three months might provide opportunities to identify and mitigate risks for opioid use disorder and overdose.

Experts noted that although there is little evidence for specific follow-up time frames, the recommendation was reasonable and reflects common practice and therefore supported both the recommendation and the category A designation. Experts further noted that social determinants of health affecting ability to return frequently for care (e.g., role as unpaid caregiver, or work at a job with minimal paid time off) or payer issues (e.g., co-pays) could have consequences when recommending frequent visits and should be considered.

Clinicians should evaluate patients to assess benefits and risks of opioids within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation. Clinicians should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased, given increased risk for overdose within the first 2 weeks of treatment (Miller et al., 2015), or when total daily opioid dosage is ≥50 MME/day, given overdose risk is doubled across multiple studies for dosages of 50 to <100 MME/day relative to <20 MME/day (see Recommendation 4). Shorter follow-up intervals (within 3 days) should be strongly considered when starting or increasing the dosage of methadone, given the variable half-life of this drug (see Recommendation 3) and the potential for drug accumulation during initiation and during upward titration of dosage. An initial follow-up interval closer to 4 weeks can be considered when starting immediate-release opioids at a dosage <50 MME/day.

In analyses of placebo-controlled trials, the clinical evidence reviews found that effects of opioids on mean improvement in pain and in function were greater at 1 to 3 months than at 3 to 6 months (Chou et al., April 2020). A cohort study found an association between longer duration of therapy and increased risk of new-onset depression (Chou et al., April 2020). Because of potential changes in the balance of benefits and risks of opioid therapy over time, clinicians should regularly reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician but on long-term opioid therapy, at least every 3 months. Clinicians seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy (see Recommendation 2). Clinicians should re-evaluate patients who are at greater risk for opioid use disorder or overdose (e.g., patients with depression or other mental health conditions, a history of substance use disorder, a history of overdose, taking ≥50 MME/day, or taking other central nervous system depressants with opioids) more frequently than every 3 months. To minimize unintended impact on patients with challenges in accessing or affording follow-up visits, practices, and health systems should work to ensure all patients can access and afford follow-up evaluation. In addition, policymakers should minimize barriers to care (e.g., through promotion of paid time off). In practice contexts where virtual visits are part of standard care (e.g., in remote areas where distance or other context makes follow-up visits challenging), follow-up assessments that allow the clinician to communicate with and observe the patient through telehealth modalities may be conducted.

At follow-up, clinicians should review patient perspectives on progress and challenges in moving toward treatment goals, determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function; whether the patient has experienced common or serious adverse events or early warning signs of serious adverse events or has signs of opioid misuse or opioid use disorder (e.g., difficulty controlling use, cravings, work, social or family problems related to opioid use); whether benefits of opioids continue to outweigh risks; and whether there is a need for opioid

dosage reduction or discontinuation. Clinicians should assess benefits in function, pain control, and quality of life by asking patients about progress toward person-centered functional goals that have meaning for them (see Recommendation 2) and/or by using tools such as the three-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale (Krebs et al., 2009); clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function (Ostelo et al., 2008). Clinicians should also ask patients about common adverse effects such as constipation and drowsiness (see Recommendation 2), as well as asking about and assessing for effects that might be early warning signs for more serious problems such as overdose (e.g., sedation or slurred speech) or opioid use disorder (e.g., craving, wanting to take opioids in greater quantities or more frequently than prescribed, difficulty controlling use, work, social, or family problems related to opioid use). Because depression, anxiety, and other psychological co-morbidities often coexist with and can interfere with resolution of pain, clinicians should use validated instruments to assess for these conditions (see Recommendation 8) and ensure that treatment for these conditions is optimized. Clinicians should ask patients about their preferences for continuing opioids, given their effects on pain and function relative to any adverse effects experienced.

If risks outweigh benefits of continued opioid therapy (e.g., if patients do not experience meaningful, sustained improvements in pain and function compared with prior to initiation of opioid therapy; if patients are taking higher-risk regimens [e.g., dosages ≥50 MME/day or opioids combined with benzodiazepines] without evidence of benefit; if patients believe benefits no longer outweigh risks; if patients request dosage reduction or discontinuation; or if patients experience overdose or other serious adverse events), clinicians should work with patients to reduce opioid dosage or to discontinue opioids when possible, using principles from Recommendation 5. Clinicians should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).

Assessing risk and addressing harms of opioid use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone when factors that increase risk for opioid overdose are present (recommendation category: A, evidence type: 4).

Implementation considerations:

- *Clinicians should offer naloxone when prescribing opioids to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients with sleep-disordered breathing, patients taking higher dosages of opioids (e.g., ≥50 MME/day), patients taking benzodiazepines with opioids (see Recommendation 11), and patients at risk for returning to a high dose to which they have lost tolerance (e.g., patients undergoing tapering or recently released from prison).*
- *Practices should provide education on overdose prevention and naloxone use to patients and offer to provide education to members of their households.*
- *Naloxone co-prescribing can be facilitated by clinics or practices with resources to provide naloxone training and by collaborative practice models with pharmacists or through standing orders for naloxone at pharmacies.*
- *Resources for prescribing naloxone in primary care and emergency department settings can be found through Prescribe to Prevent at http://prescribetoprevent.org; additional resources are at https://samhsa.gov.*
- *In part because of concerns about cost of naloxone and access for some patients, this recommendation specifies that naloxone should be "offered" to patients. Clinicians, health systems, and payers should work to ensure patients can access naloxone, a potentially lifesaving treatment.*
- *Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing when possible to minimize risks for opioid overdose.*
- *When making decisions about whether to initiate opioid therapy for pain during pregnancy, clinicians and patients together should carefully weigh benefits and risks. For pregnant people already receiving opioids, clinicians should access appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal (see Recommendation 5).*
- *For pregnant people with opioid use disorder, medications for opioid use disorder (buprenorphine or methadone) have been associated with improved maternal outcomes and should be offered (see Recommendation 12).*

- *Clinicians should use additional caution and increased monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency and for patients aged ≥65 years and should implement interventions to mitigate common risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.*
- *Clinicians should ensure that treatment for depression and other mental health conditions is optimized, consulting with behavioral health specialists when needed.*
- *Clinicians should ask patients about their drug and alcohol use.*
- *Clinicians should use PDMP data (see Recommendation 9) and toxicology screening (see Recommendation 10) as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and overdose.*
- *Clinicians should provide specific counseling on increased risks for overdose when opioids are combined with other drugs or alcohol (see Recommendation 2) and ensure that patients are provided or receive effective treatment for substance use disorders when needed (see Recommendation 12).*
- *Although substance use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. See "Pain management for patients with opioid use disorder" section of Recommendation 12 for additional considerations specific to patients with pain and opioid use disorder.*
- *If clinicians consider opioid therapy for chronic pain for patients with substance use disorder, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and incorporate strategies to mitigate risk into the management plan, such as offering naloxone (see Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present) and increasing frequency of monitoring (see Recommendation 7).*
- *If patients experience nonfatal opioid overdose, clinicians should evaluate for opioid use disorder and treat or arrange treatment if needed. Clinicians should work with patients to reduce opioid dosage and to discontinue opioids when indicated (see Recommendation 5) and should ensure continued close monitoring and support for patients prescribed or not prescribed opioids.*

  If clinicians continue opioid therapy in patients with prior opioid overdose, they should discuss increased risks for overdose with patients, carefully consider whether benefits of opioids outweigh substantial risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone and increasing frequency of monitoring (see Recommendation 7).

Supporting Rationale

The clinical evidence reviews found evidence too limited to determine effects of patient demographics and comorbidities on risk of opioid-related harms (Chou et al., April 2020). However, based on observational studies and expert opinion, certain risk factors are likely to increase

susceptibility to opioid-related harms and warrant incorporation of additional strategies into the management plan to mitigate risk. Clinicians should assess these risk factors periodically, with frequency individualized to patient comorbidities and other risk factors. For example, factors that vary more frequently over time, such as alcohol use, require more frequent assessment. In addition, clinicians should offer naloxone and re-evaluate patients more frequently (see Recommendation 7) when factors that increase risk for harm, such as sleep-disordered breathing, history of overdose, history of substance use disorder, higher dosages of opioids (e.g., ≥50 MME/day), and concurrent use of benzodiazepines with opioids, are present. Experts noted concerns with potential downstream effects of offering naloxone for patients of limited means to afford the cost of purchasing naloxone. In part because of this concern, and also because in some settings, naloxone is directly provided by a practice or health system to patients, "offering" naloxone is recommended. Clinicians, health systems, and payers should work to ensure patients can access naloxone, a potentially lifesaving treatment.

Patients with sleep-disordered breathing, including sleep apnea

A case-control analysis among Veterans prescribed opioids found that sleep apnea and chronic pulmonary disease were associated with increased risk for life-threatening respiratory central nervous system depression or overdose (Zedler et al., 2014). Careful monitoring and cautious dose titration should be used if opioids are prescribed for patients with mild sleep-disordered breathing. Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing, whenever possible, to minimize risks for opioid overdose.

Pregnant people

Opioids used during pregnancy might be associated with risks to both parent and fetus. Some studies have shown an association of opioid use in pregnancy with stillbirth, poor fetal growth, pre-term delivery, and birth defects (Broussard et al., 2011; Lind et al., 2017; Whiteman et al., 2014; Yazdy, Desai,

& Brogly, 2015; Yazdy, Mitchell, Tinker, Parker, & Werler, 2013). In some cases, opioid use during pregnancy leads to neonatal opioid withdrawal syndrome (Hadi, da Silva, Natale, Boyd, & Morley-Forster, 2006). At the same time, as noted by the American College of Obstetricians and Gynecologists, "a cautious approach to prescribing opioids should be balanced with the need to address pain… Pregnancy should not be a reason to avoid treating acute pain" ("Committee Opinion No. 711: Opioid Use and Opioid Use Disorder in Pregnancy," 2017). Clinicians and patients together should carefully weigh benefits and risks when making decisions about whether to initiate opioid therapy for pain during pregnancy. In addition, before initiating opioid therapy for individuals who can become pregnant, clinicians should discuss family planning and how long-term opioid use might affect any future pregnancy. When opioids are needed for treatment of acute pain in pregnant people, the lowest dose to achieve expected effects (see Recommendation 4) should be used for no longer than the expected duration of pain severe enough to require opioids (see Recommendation 6). For pregnant people with chronic pain, the American College of Obstetricians and Gynecologists recommends that "practice goals include strategies to avoid or minimize the use of opioids for pain management, highlighting alternative pain therapies such as nonpharmacologic (e.g., exercise, physical therapy, behavioral approaches), and nonopioid pharmacologic treatments" ("Committee Opinion No. 711: Opioid Use and Opioid Use Disorder in Pregnancy," 2017). For pregnant people already receiving opioids, clinicians should access appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal (see Recommendation 5).

The American College of Obstetricians and Gynecologists notes that early universal screening, brief intervention (e.g., engaging in a short conversation, providing feedback and advice), and referral for treatment of pregnant people with opioid use disorder improve both maternal and infant outcomes (The American College of Obstetricians and Gynecologists Committee on Obstetric Practice & American Society of Addiction Medicine, 2017). For pregnant people with opioid use disorder, medications for

opioid use disorder (buprenorphine or methadone) have been associated with improved maternal outcomes and should be offered (The American College of Obstetricians and Gynecologists Committee on Obstetric Practice & American Society of Addiction Medicine, 2017) (see Recommendation 12).

The American Academy of Pediatrics has published recommendations for the care of infants with neonatal opioid withdrawal syndrome, including that pregnant people with opioid use disorder should receive antenatal counseling to provide education on the clinical signs of withdrawal and enhance maternal understanding of postnatal treatment for neonatal opioid withdrawal syndrome (e.g., nonpharmacologic treatment including breastfeeding, and pharmacotherapy) and that all infants with long-term opioid exposure should be observed for at least 72 hours (4 to 7 days if exposed to buprenorphine or sustained released opioids and 5 to 7 days if exposed to methadone) to monitor for the development of withdrawal (Patrick, Barfield, & Poindexter, 2020). Clinicians caring for pregnant people receiving opioids for pain or receiving buprenorphine or methadone for opioid use disorder should arrange for delivery at a facility prepared to monitor, evaluate for, and treat neonatal opioid withdrawal syndrome. In instances when travel to such a facility would present an undue burden on the pregnant person, it is appropriate to deliver locally, monitor and evaluate the newborn for neonatal opioid withdrawal syndrome, and transfer the newborn for additional treatment if needed. Previous guidelines have recommended that codeine be avoided whenever possible among mothers who are breastfeeding and, if used, should be limited to the lowest possible dose and to a 4-day supply with re-evaluation thereafter (National Opioid Use Guideline Group, 2010).

Patients with renal or hepatic insufficiency

A case-control study of risk of life-threatening respiratory central nervous system depression or overdose among veterans prescribed opioids found that renal disease and moderate or severe liver disease were associated with increased risk for life-threatening respiratory central nervous system depression or overdose (Zedler et al., 2014). Clinicians should use additional caution and increased

monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency, given their decreased ability to process and excrete medications, susceptibility to accumulation of opioids, and reduced therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (*Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 9th ed*, 1996) (see Recommendations 3, 4, and 7).

Patients aged ≥65 years

Persons aged ≥65 years can be at risk for inadequate pain treatment (Becker et al., 2017; Bernabei et al., 1998; Institute of Medicine Committee on Advancing Pain Research Care and Education, 2011; U.S. Department of Health and Human Services, 2019b). Older adults can also be at risk for changes in function that might be exacerbated by pain and contribute to deterioration in overall health and independence. Pain management for older patients can be challenging given increased risks of both nonopioid pharmacologic therapies (see Recommendation 2) and opioid therapy in this population. A case-control analysis among Veterans prescribed opioids found that age >55 years was associated with increased risk for life-threatening respiratory central nervous system depression or overdose (Zedler et al., 2014). Given reduced renal function and medication clearance even in the absence of renal disease, patients aged ≥65 years might have increased susceptibility to accumulation of opioids and a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (*Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 9th ed*, 1996). Some older adults might have a cognitive impairment, such as dementia, which can increase risk for medication errors and make opioid-related confusion riskier. In addition, older adults are more likely than younger adults to experience co-morbid medical conditions and more likely to receive multiple medications, some of which might interact with opioids. Functional assessment is especially important in patients aged ≥65 years to better assess impact of pain on function and independence. Clinicians should use additional caution and increased monitoring (see Recommendation 7) for patients aged ≥65 years to

ensure pain is addressed and to minimize risks of opioids prescribed and should educate older adults receiving opioids to avoid medication-related behaviors that increase risk such as saving unused medications. Clinicians should also implement interventions to mitigate common risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.

Patients with mental health conditions

Because psychological distress frequently interferes with improvement of pain and function in patients with chronic pain, using validated instruments such as the Generalized Anxiety Disorder (GAD)-7 and the Patient Health Questionnaire (PHQ)-9 or the PHQ-4 to support assessment for anxiety, post-traumatic stress disorder, and/or depression (Kroenke, Spitzer, Williams, & Löwe, 2010) might help clinicians improve overall pain treatment outcomes. Additional caution and increased monitoring (see Recommendation 7) might lessen the increased risk for overdose among patients with depression (Turner & Liang, 2015; Zedler et al., 2014). Previous guidelines have noted that acute psychiatric instability (severe depression, unstable bipolar disorder, or unstable psychotic disorder) or intermediate to high acute suicide risk precludes the safe use of self-administered long-term opioid therapy and that treatment for chronic pain with movement, exercise and cognitive behavioral therapy for pain may have benefit in treating depression, PTSD, and in reducing suicide risk (U.S. Department of Veterans Affairs and Department of Defense, 2017). In addition, patients with anxiety disorders and other mental health conditions are more likely to receive benzodiazepines, which can exacerbate opioid-induced respiratory depression and increase risk for overdose (see Recommendation 11). Clinicians should ensure that treatment for depression and other mental health conditions as well as treatment for pain is optimized, consulting with behavioral health specialists when needed. Treatment for depression can improve pain symptoms as well as depression and might decrease overdose risk (Turner & Liang, 2015). For treatment of chronic pain in patients with depression, clinicians should consider using tricyclic or SNRI

antidepressants for analgesic as well as antidepressant effects if these medications are not otherwise contraindicated (see Recommendation 2).

Patients with substance use disorders

Patients with substance use disorders including alcohol use disorder are likely to experience greater risks for opioid use disorder and overdose (Bohnert et al., 2011; Dunn et al., 2010; Zedler et al., 2014) than persons without these conditions. Despite increased risk for opioid misuse and opioid use disorder when prescribed opioid analgesics (Edlund, Steffick, Hudson, Harris, & Sullivan, 2007; Reid et al., 2002), patients with histories of substance use disorders are more likely than other patients to receive long-term opioid treatment for chronic pain (Edlund et al., 2010). Previous guidelines have recommended screening or risk assessment tools to identify patients at higher risk for opioid misuse or opioid use disorder. However, the clinical evidence reviews found that currently available risk stratification tools (e.g., Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain Version 1, SOAPP-R, and Brief Risk Interview) show limited and variable accuracy for classification of patients as at low or high risk for opioid use disorder or misuse (Chou et al., April 2020). If these tools are used, they should be supplemented with other assessments, such as discussions with patients, family, and caregivers, clinical records, PDMP data (see Recommendation 9), and toxicology screening data (see Recommendation 10). Clinicians should always exercise caution when considering or prescribing opioids and should not overestimate the ability of currently available risk stratification tools to rule out risks from long-term opioid therapy.

Non-prescribed drugs (e.g., heroin, illicitly manufactured fentanyl, cocaine, methamphetamine) (Gladden, O'Donnell, Mattson, & Seth, 2019) and alcohol (Jones, Paulozzi, & Mack, 2014) are listed as contributory factors on a substantial proportion of death certificates for prescription opioid-involved overdose deaths. Clinicians should ask patients about their drug (U.S. Preventive Services Task Force, 2020) and alcohol use. Single screening questions can be used (Saitz, Cheng, Allensworth-Davies, Winter,

& Smith, 2014). For example, the question "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" (with an answer of one or more considered positive) was found in a primary care setting to be 100% sensitive and 73.5% specific for the detection of a drug use disorder compared with a standardized diagnostic interview (P. C. Smith, Schmidt, Allensworth-Davies, & Saitz, 2010). Validated screening tools such as the Drug Abuse Screening Test (DAST) (Yudko, Lozhkina, & Fouts, 2007), the Tobacco, Alcohol, Prescription medication, and other Substance use Tool (TAPS) (McNeely et al., 2016), and the Alcohol Use Disorders Identification Test (AUDIT) (Reinert & Allen, 2007) can also be used. Clinicians should use PDMP data (see Recommendation 9) and toxicology screening (see Recommendation 10) as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and overdose. Clinicians should also provide specific counseling on increased risks for overdose when opioids are combined with other drugs or alcohol (see Recommendation 2) and ensure that patients receive effective treatment for substance use disorders when needed (see Recommendation 12).

If clinicians consider opioid therapy for chronic pain, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and incorporate strategies to mitigate risk into the management plan, such as offering naloxone (see Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed. Clinicians should communicate with patients' substance use disorder treatment providers if opioids are prescribed. Although substance use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. See "Pain management for patients with opioid use disorder" section of Recommendation 12 for additional considerations specific to patients with opioid use disorder.

Patients with prior nonfatal overdose

Prior nonfatal overdose is associated with substantially increased risk for future nonfatal or fatal opioid overdose (M. R. Larochelle, Liebschutz, Zhang, Ross-Degnan, & Wharam, 2016). Yet, a cohort study of commercially insured patients found that opioids were dispensed to 91% of patients after an overdose, and a substantial percentage experienced a repeated opioid overdose, with a cumulative incidence at 2 years of 17% among patients receiving 100 or more MME/day, 15% among those prescribed 50 to 100 MME/day, 9% among those prescribed <50 MME/day, and 8% among those prescribed no opioids (M. R. Larochelle et al., 2016).

If patients experience nonfatal opioid overdose, clinicians should evaluate for opioid use disorder and treat or arrange treatment if needed. Buprenorphine or methadone for opioid use disorder following nonfatal overdose are associated with reduced all-cause and opioid-related mortality (Marc R Larochelle et al., 2018). Clinicians should work with patients to reduce opioid dosage and to discontinue opioids when indicated (see Recommendation 5) and should ensure continued close monitoring and support for patients prescribed or not prescribed opioids. If clinicians continue opioid therapy in patients with prior opioid overdose, they should discuss increased risks for overdose with patients, carefully consider whether benefits of opioids outweigh substantial risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone (see Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present), involving patient-identified trusted family members, and increasing frequency of monitoring (see Recommendation 7).

Offering naloxone to patients when factors that increase risk for opioid-related harms are present

Naloxone is an opioid antagonist that can reverse severe respiratory depression; its administration by laypersons, such as friends, family, and caregivers of persons who experience opioid overdose, can save lives (Walley et al., 2013). Naloxone precipitates acute withdrawal among patients physically dependent on opioids. Serious adverse effects, such as pulmonary edema, cardiovascular

instability, and seizures, have been reported but are rare at doses consistent with labeled use for opioid overdose (Enteen et al., 2010). The clinical evidence reviews identified one observational study (Coffin et al., 2016) finding that provision of naloxone to patients prescribed opioids in primary care clinics was associated with decreased likelihood of emergency department visits (but no difference in risk of overdose) (Chou et al., April 2020).

Clinicians should offer naloxone when prescribing opioids to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients taking benzodiazepines with opioids (see Recommendation 11)***, patients at risk for returning to a high dose to which they have lost tolerance (e.g., patients undergoing tapering or recently released from prison), and patients taking higher dosages of opioids (≥50 MME/day).*** Practices should provide education on overdose prevention and naloxone use to patients receiving naloxone prescriptions and to members of their households. Naloxone co-prescribing can be facilitated by clinics or practices with resources to provide naloxone training and by collaborative practice models with pharmacists. Resources for prescribing naloxone in primary care settings can be found through Prescribe to Prevent at http://prescribetoprevent.org.

9. When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, 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 combinations that put the patient at high risk for overdose (recommendation category: B, evidence type: 4).

Implementation considerations:

- *Ideally, PDMP data should be reviewed before every opioid prescription for acute, subacute, or chronic pain. This is recommended in all jurisdictions where PDMP availability and access policies, as well as clinical practice settings, make this practicable (e.g., clinician and delegate access permitted).*

- *At a minimum, during long-term opioid therapy, PDMP data should be reviewed before an initial opioid prescription and then every 3 months or more frequently. The recommendation category B acknowledges variation in PDMP availability and circumstances. However, because PDMP information can be most helpful when results are unexpected, and to minimize bias in application, clinicians should apply this recommendation when feasible to all patients rather than differentially based on assumptions about what they will learn about different patients.*

- *Clinicians should use specific PDMP information about medications prescribed to their patient in the context of other clinical information, including their patient's history, physical findings, and other relevant testing, in order to help them communicate with and protect their patient.*

- *Clinicians should review PDMP data specifically for prescription opioids and other controlled medications patients have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or combinations (e.g., opioids combined with benzodiazepines) that put the patient at high risk for overdose.*

- *PDMP-generated risk scores have not been validated against clinical outcomes such as overdose and should not take the place of clinical judgment. Clinicians should not dismiss patients from their practice on the basis of PDMP information. Doing so can adversely affect patient safety, could represent patient abandonment, and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of prescription opioids and overdose prevention) and interventions (e.g., safer prescriptions, nonopioid pain treatment [see Recommendations 1 and 2], naloxone [see Recommendation 8], and effective treatment for substance use disorder [see Recommendations 8 and 12]).*

- *Clinicians should take actions to improve patient safety:*

    - *Discuss information from the PDMP with their patient and confirm that the patient is aware of any additional prescriptions. Occasionally, PDMP information can be incorrect (e.g., if the wrong name or birthdate has been entered, the patient uses a nickname or maiden name, or another person has used the patient's identity to obtain prescriptions).*

    - *Discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving prescription opioids from more than one clinician or receiving medications that increase risk when combined with opioids (e.g., benzodiazepines; see Recommendation 11) and offer naloxone (see Recommendation 8).*

    - *Use extreme caution when prescribing opioids and benzodiazepines concurrently, appreciating that some patient circumstances warrant prescribing of these medications concomitantly. 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 (see Recommendation 11).*

    - *Consider the total MME/day for concurrent opioid prescriptions to help assess the patient's overdose risk (see Recommendation 4). Buprenorphine should not be counted in the total MME/day in calculations given its opioid partial agonist properties that confer a ceiling effect on respiratory depression. If patients are found to be receiving high total daily dosages of opioids, discuss safety concerns with the patient, consider in collaboration with the*

patient if tapering to a safer dosage is warranted (see Recommendation 5), and offer naloxone (see Recommendation 8).

- *Discuss safety concerns with other clinicians who are prescribing controlled substances for their patient. Ideally, clinicians should first discuss concerns with their patient and inform him or her that they plan to coordinate care with the patient's other clinicians to improve the patient's safety.*

- *Screen for substance use and discuss concerns with their patient (see Recommendations 8 and 12).*

If clinicians believe their patient might be diverting (sharing or selling prescription opioids and not taking them), consider toxicology testing to assist in determining whether prescription opioids can be discontinued without causing withdrawal (see Recommendations 5 and 10). A negative toxicology test for prescribed opioids might indicate the patient is not taking prescribed opioids, although clinicians should consider other possible reasons for this test result, such as false negative results or misinterpretation of results (see Recommendation 10).

Supporting Rationale

PDMPs are databases overseen by states, territories, counties, and the District of Columbia that collect information on controlled prescription drugs dispensed by pharmacies in most jurisdictions and, in select jurisdictions, by dispensing clinicians as well. The clinical evidence reviews did not find studies evaluating the effectiveness of PDMPs for risk mitigation. However, among patients receiving concurrent treatment with opioids and benzodiazepines, overdose risk is further increased among patients receiving these treatments from multiple prescribers rather than one prescriber, highlighting potential room for improvement in care coordination (K. P. Chua, Brummett, Ng, & Bohnert, 2021). PDMP data also can be helpful when patient medication history is not otherwise available (e.g., for patients from other locales) and when patients transition care to a new clinician. A contextual evidence review (Chou et al., April 2020) identified a survey of physicians in Maryland (D. H. Lin et al., 2017) finding that while barriers towards PDMP review were noted, including not knowing about the program, registration difficulties, and difficulty accessing data, most participants felt that PDMPs improved opioid prescribing by decreasing opioid prescription amounts and increasing comfort with prescribing opioids

(Chou et al., April 2020). Integration of PDMPs with electronic health records (EHRs) can reduce burden on clinicians compared to having to access a separate system (Centers for Disease Control and Prevention, 2017; U.S. Government Accountability Office, 2020). Special attention should be paid to ensure that PDMP information is not used in a way that is harmful to patients. For example, PDMP information has been used to dismiss patients from clinician practices (Irvine et al., 2014), which might adversely affect patient safety and result in untreated or undertreated pain. Many state laws require PDMP use under specific circumstances (B. Lee, Zhao, Yang, Ahn, & Perry, 2021). Experts noted concern about PDMP risk scores or other algorithmic interpretations from software platforms that can lead to distrust between clinicians and patients and stigmatization, particularly for patients with conditions such as opioid use disorder. Risk scores are reportedly generated by applying trade secret-protected algorithms to information from patient EHRs and other sources such as court records and criminal and sexual trauma histories; these algorithms may disparately impact women, people of color, and people who live in poverty (J. Oliva, 2021). Importantly, while one PDMP-generated risk measure has shown fair concurrence with the WHO Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), these scores have not been externally validated against clinical outcomes (Cochran et al., 2021) (J. Oliva, 2021). Such risk scores should not take the place of clinical judgment. Rather, clinicians should use specific PDMP information about medications prescribed to their patient in the context of other clinical information, including their patient's history, physical findings, and other relevant testing, in order to help them communicate with and protect their patient. Experts raised varying points regarding frequency of PDMP use, with many agreeing PDMPs should be consulted prior to every opioid prescription, several agreeing that universal application would mitigate bias in application to different patients, and others believing it might not be warranted or feasible to check the PDMP in all cases, particularly prior to prescribing opioids for acute pain for a small number of days. Ideally, PDMP data should be reviewed before every opioid prescription for acute, subacute, or chronic pain. This is

recommended in all jurisdictions where PDMP availability and access policies make this practicable (e.g., clinician and delegate access permitted). At a minimum, PDMP data should be reviewed before initial opioid prescriptions for subacute or chronic pain and then every 3 months or more frequently during long-term opioid therapy. The recommendation category B acknowledges variation in PDMP availability (PDMPs now exist in most but not all U.S. jurisdictions) and circumstances (e.g., a clinician might reasonably determine that a patient with severe acute pain presenting in the emergency department during a PDMP system access failure would be adversely impacted by waiting hours for a prescription). However, because PDMP information can be most helpful when results are unexpected, and to minimize bias in application, clinicians should apply this recommendation when feasible to all patients rather than differentially based on assumptions about what they will learn about specific patients.

Clinicians should review PDMP data for prescription opioids and other controlled medications patients might have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or combinations (e.g., opioids combined with benzodiazepines) that put the patient at high risk for overdose. If patients are found to have high opioid dosages or combinations of medications that might put them at risk for overdose, or multiple controlled substance prescriptions written by different clinicians, clinicians should take actions to improve patient safety (see above Implementation Considerations).

10. When prescribing opioids for subacute or chronic pain, clinicians should consider toxicology testing to assess for prescribed medications as well as other prescribed and non-prescribed controlled substances (recommendation category: B, evidence type: 4).

Implementation considerations:

- *Clinicians should not dismiss patients from care based on a toxicology test result because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids or other drugs from alternative sources and the clinician missing opportunities to facilitate treatment for substance use disorder.*

- *Prior to starting opioids and periodically during opioid therapy, clinicians should consider toxicology testing to assess for prescribed opioids as well as other prescription and nonprescription controlled substances that increase risk for overdose when combined with opioids, including nonprescribed and illicit opioids and benzodiazepines.*
- *Clinicians, practices, and health systems should aim to minimize bias testing and should not apply this recommendation differentially based on assumptions about what they will learn about different patients.*
- *Predicting risk is challenging, and currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use or substance use disorder. Rather, clinicians should consider toxicology screening results as potentially useful data, in the context of other clinical information, for all patients, and consider toxicology screening whenever its potential problems can be mitigated.*
- *Clinicians should explain to patients that toxicology testing will not be used to dismiss patients from care and is intended to improve their safety.*
- *Clinicians should explain expected results (e.g., presence of prescribed medication and absence of drugs, including non-prescribed controlled substances, not reported by the patient) and ask patients about use of prescribed and other drugs and whether there might be unexpected results.*
- *Toxicology screening can be performed with a relatively inexpensive presumptive immunoassay panel that tests for opiates as a class, benzodiazepines as a class, and several non-prescribed substances.*
- *The use of confirmatory testing can add substantial costs and should be based on the need to detect specific opioids, such as those that are being prescribed, and those that cannot be identified on standard immunoassays or on the presence of unexpected toxicology test results.*
- *Clinicians should be familiar with the drugs included in toxicology screening panels used in their practice and should understand how to interpret results for these drugs. For example, a positive "opiates" immunoassay detects morphine, which might reflect patient use of morphine, codeine, or heroin, but does not detect synthetic opioids and might not detect semisynthetic opioids. In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is taking and might not mean the patient is taking the specific opioid for which the test was positive.*
- *Restricting confirmatory testing to situations and substances for which results can reasonably be expected to affect patient management can reduce costs of toxicology testing.*
- *Clinicians may wish to discuss unexpected results with the local laboratory or toxicologist and should discuss unexpected results 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. For example, a patient might explain that the test is negative for prescribed opioids because she felt opioids were no longer helping and discontinued them. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (e.g., gas or liquid chromatography/mass spectrometry) might be warranted.*

- *Clinicians should use unexpected results to improve patient safety (e.g., change pain management strategy [see Recommendation 2], carefully weigh benefits and risks of reducing or continuing opioid dosage [see Recommendation 5], re-evaluate more frequently [see Recommendation 7], offer naloxone [see Recommendation 8], offer or refer for substance use disorder treatment [see Recommendation 12], all as appropriate).*

Supporting Rationale

The clinical evidence reviews did not find studies evaluating the effectiveness of toxicology screening for risk mitigation during opioid prescribing for pain. However, concurrent use of opioid pain medications with other opioid pain medications, benzodiazepines, or heroin or other non-pharmaceutical opioids can increase patients' risk for overdose. Toxicology tests can provide information about drug use that is not reported by the patient. In addition, toxicology tests can assist clinicians in identifying when patients are not taking opioids prescribed for them, which might in some cases indicate diversion or other clinically important issues such as difficulties with adverse effects. The most commonly drug-tested bodily specimen is urine; oral fluid (saliva) testing is also available (Cone & Huestis, 2007), but testing protocols using oral fluid are not as well-established. On October 25, 2019, SAMHSA published guidelines for the inclusion of oral fluid specimens in federal executive branch agencies' toxicology testing programs (Substance Abuse and Mental Health Services Administration, 2019), effective January 1, 2020. Toxicology testing results can be associated with outcomes and practices that harm patients (e.g., stigmatization, inappropriate termination from care). False positive and false negative presumptive results are not uncommon, a problem which can be compounded because clinicians commonly misinterpret results (I. Chua et al., 2020; Starrels, Fox, Kunins, & Cunningham, 2012), leading to inappropriate consequences for patients. Urine toxicology tests do not provide accurate information about how much or what dose of opioids or other drugs a patient took. Testing for fentanyl is not currently available in widely-used toxicology assays, potentially leading to false assurance. Ideally, clinicians would only test for substances for which results could affect patient management. However, it can be challenging or impossible for clinicians to tailor widely used toxicology

panels to include the specific substances most relevant to clinical decisions for their patient. Toxicology testing costs are not always covered fully by insurance and can be a burden for patients, and clinician time is needed to interpret, confirm, and communicate results.

Experts noted concerns that biases and disparities affecting which patients have toxicology tests could have disproportionately negative consequences among Black and Latinx patients. In addition, testing costs would have the greatest consequences for patients with the least ability to pay. Because of these concerns, some experts felt grading the recommendation as category A could potentially reduce bias and disparities. However, others thought that while universal application could mitigate bias in who is tested, it would not mitigate stigma associated with testing. In addition, experts noted concerns about accuracy, clinician interpretation, testing costs, and potential for a wait for test results to delay care.

Because of concerns about imperfect accuracy, problems in interpretation, potential stigma, and cost, the recommendation is rated category B. However, clinicians, practices, and health systems should aim to minimize bias in its application and should not apply this recommendation differentially based on assumptions about what they will learn about different patients. Predicting risk is challenging, and currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use disorder (Chou et al., April 2020). Rather, clinicians should consider toxicology test results as potentially useful data, in the context of other clinical information, for all patients, and consider toxicology testing whenever its potential problems can be mitigated. For example, clinicians can become familiar with the drugs included in toxicology testing panels used in their practice and understand how to interpret results, and practices and health systems can ensure a laboratorian or toxicologist is available to discuss unexpected results, that costs to patients are not burdensome, and that practice policies regarding testing and frequency can minimize bias. For example, routine use of testing with standardized policies at the practice or clinic level might help destigmatize their use. Because truly

random testing might not be feasible in clinical practice, some clinics obtain a specimen at every visit, but only send it for testing on a random schedule.

Prior to starting opioids and periodically during opioid therapy, clinicians should consider toxicology testing to assess for prescribed opioids as well as other prescription and non-prescribed substances that increase risk for overdose when combined with opioids, including non-prescribed and illicit opioids and benzodiazepines. Before ordering toxicology testing, clinicians should have a plan for responding to unexpected results. Clinicians should explain to patients that toxicology testing will not be used punitively (e.g., will not be used to dismiss patients from care) and is intended to improve their safety. Clinicians should also explain expected results (e.g., presence of prescribed medication and absence of substances, including non-prescribed substances, not reported by the patient). Clinicians should ask patients about use of prescribed medications and other substances and ask whether there might be unexpected results. This will provide an opportunity for patients to provide information about changes in their use of prescribed opioids or other drugs.

In most situations, initial toxicology testing can be performed with a relatively inexpensive immunoassay panel that tests for opiates and benzodiazepines as classes, and several non-prescribed substances. Patients prescribed oxycodone or non-morphine-based opioids (e.g., buprenorphine, methadone) require specific testing for those agents. The use of confirmatory testing can add substantial costs and should be based on the need to detect the specific opioid that is prescribed and those that cannot be identified on standard immunoassays or on the presence of unexpected toxicology test results. Clinicians and health systems should work to minimize inequitable cost burdens for patients and limit specific testing to situations when it is necessary. Clinicians should be familiar with the compounds included in toxicology testing panels used in their practice and should understand how to interpret results. For example, a positive opiate immunoassay test result detects morphine, which might reflect patient use of morphine, codeine, or heroin, but this immunoassay does not detect synthetic

opioids (e.g., fentanyl or methadone) and might not detect semisynthetic opioids (e.g., oxycodone or buprenorphine). Many laboratories use an oxycodone immunoassay that detects oxycodone and oxymorphone, but these may need to be ordered or identified separately in a toxicology testing panel. In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is taking and might not mean the patient is taking the specific opioid for which the test was positive. For example, hydromorphone is a metabolite of hydrocodone, and oxymorphone is a metabolite of oxycodone. Detailed considerations for interpretation of urine toxicology test results, including which tests to order and expected results, drug detection time in urine, and drug metabolism have been published previously (Washington State Agency Medical Directors' Group, 2015). A review including interpretation of oral fluid sample toxicology test results is also available (Cone & Huestis, 2007). Restricting confirmatory testing to situations and substances for which results can reasonably be expected to affect patient management can reduce costs of toxicology testing, given the substantial costs associated with confirmatory testing methods.

Clinicians may wish to discuss unexpected results with the local laboratory or toxicologist and should discuss unexpected results 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. For example, a patient might explain that the test is negative for prescribed opioids because she felt opioids were no longer helping and discontinued them. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (e.g., gas or liquid chromatography/mass spectrometry) might be warranted to clarify the situation.

Clinicians should use unexpected results to improve patient safety (e.g., change pain management strategy [see Recommendation 2], carefully weigh benefits and risks of reducing or continuing opioid dosage [see Recommendation 5], re-evaluate more frequently [see Recommendation

7], offer naloxone [see Recommendation 8], offer or refer for substance use disorder treatment [see Recommendation 12], all as appropriate). If tests for prescribed opioids are repeatedly negative, including confirmatory tests, and the clinician has verified that the patient is not taking the prescribed opioid, clinicians can discontinue the prescription without a taper and discuss options for safe disposal of unused opioids (U.S. Food and Drug Administration, 2020a).

Clinicians should not dismiss patients from care based on a toxicology test result because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids from alternative sources and the clinician missing opportunities to facilitate treatment for substance use disorder.

11. Clinicians should use extreme caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants (recommendation category: B, evidence type: 3).

Implementation considerations:

- *Although there are circumstances when it might be appropriate to prescribe opioids to a patient who is also prescribed benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should use extreme caution when prescribing opioids and benzodiazepines concurrently. In addition, clinicians should consider whether benefits outweigh risks of concurrent use of opioids with other central nervous system depressants (e.g., muscle relaxants, non-benzodiazepine sedative hypnotics, potentially sedating anticonvulsant medications such as gabapentin and pregabalin).*

- *Clinicians should check the PDMP for concurrent controlled medications prescribed by other clinicians (see Recommendation 9) and should consider involving pharmacists as part of the management team when opioids are co-prescribed with other central nervous system depressants.*

- *In patients receiving opioids and benzodiazepines long-term, clinicians should carefully weigh the benefits and risks of continuing therapy with opioids and benzodiazepines and discuss with patients and other members of the patient's care team.*

- *Risks of concurrent opioid and benzodiazepine use are likely to be greater with unpredictable use of either medication, with use of high-dose opioids and high-dose benzodiazepines in combination, or with use with other substances including alcohol (as compared to long-term stable use of low-dose opioids and low-dose benzodiazepines without other substances).*

- *In specific situations, benzodiazepines can be beneficial, and stopping benzodiazepines can be destabilizing.*

- *Buprenorphine or methadone for opioid use disorder should not be withheld from patients taking benzodiazepines or other medications that depress the central nervous system.*

- *If risks are determined to outweigh benefits of continuing opioid and benzodiazepine therapy at current dosages and a decision is made to taper, it might be safer and more practical to taper opioids first. There can be greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and tapering opioids can be associated with anxiety (see Recommendation 5).*

- *Clinicians should taper benzodiazepines gradually prior to discontinuation because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death. The rate of tapering should be individualized.*

- *If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific antidepressants or other nonbenzodiazepine medications approved for anxiety should be offered.*

- *Clinicians should communicate with clinicians managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.*

Supporting Rationale

Benzodiazepines and opioids both cause central nervous system depression, and benzodiazepines can potentiate opioid-induced decreases in respiratory drive. Epidemiologic studies find concurrent benzodiazepine use in large proportions of opioid-related overdose deaths (Dasgupta et al., 2016; Gomes et al., 2011; Jones & McAninch, 2015). The clinical evidence reviews identified 3 cohort studies finding an association between concurrent use of benzodiazepines and opioids versus opioids alone and increased risk of overdose (Chou et al., April 2020). A case-cohort study found concurrent benzodiazepine prescription with opioid prescription to be associated with a near-quadrupling of risk for overdose death compared with opioid prescription alone (Park, Saitz, Ganoczy, Ilgen, & Bohnert, 2015).

The clinical evidence reviews did not find studies evaluating the effectiveness of avoiding co-prescribing of benzodiazepines and opioids on risk of overdose (Chou et al., April 2020). The clinical evidence reviews additionally identified 3 observational studies finding an association between concurrent use of gabapentinoids and opioids versus opioids alone and increased risk of overdose, with higher risks at increased gabapentinoid doses (Chou et al., April 2020).

Experts noted that rather than necessarily being a direct cause of overdose, benzodiazepines might serve as a marker for risk of overdose due to underlying conditions, that–in specific situations– benzodiazepines can be beneficial, and that stopping benzodiazepines can be destabilizing. In addition, experts noted that long-term, stable use might be safer than erratic, unpredictable use. Due to these considerations, several experts felt recommending extreme caution with concurrent prescription of opioids and benzodiazepines was more appropriate than a recommendation to avoid prescribing opioid pain medication and benzodiazepines concurrently and that category B would be more appropriate than category A for this recommendation.

Although there are circumstances when it might be appropriate to prescribe opioids to a patient receiving benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should use extreme caution when prescribing opioids and benzodiazepines concurrently. In addition, given that other central nervous system depressants (e.g., muscle relaxants, non-benzodiazepine sedative hypnotics, potentially sedating anticonvulsant medications such as gabapentin and pregabalin) (U.S. Food and Drug Administration, 2019b) can potentiate respiratory depression associated with opioids, clinicians should consider whether benefits outweigh risks of concurrent use of these medications. Clinicians should check the PDMP for concurrent controlled medications prescribed by other clinicians (see Recommendation 9) and should consider involving pharmacists as part of the management team when opioids are co-prescribed with other central nervous system depressants.

In patients receiving opioids and benzodiazepines long-term, clinicians should carefully weigh the benefits and risks of continuing therapy with opioids and benzodiazepines and discuss with patients and other members of the patient's care team. In specific situations, benzodiazepines can be beneficial, and stopping benzodiazepines can be destabilizing. Importantly, as emphasized in an FDA advisory (U.S. Food and Drug Administration, 2017), buprenorphine or methadone for opioid use disorder should not be withheld from patients taking benzodiazepines or other medications that depress the central nervous system. While the combined use of these medications increases risks, the harm caused by untreated opioid use disorder can outweigh these risks.

If risks are determined to outweigh benefits of continuing opioids for pain and benzodiazepine therapy at current dosages and a decision is made to taper one or more medications, it might be safer and more practical to taper opioids first (see Recommendation 5). There can be greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and tapering opioids can be associated with anxiety. Clinicians should taper benzodiazepines gradually prior to discontinuation because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death (Haque et al., 1990; Lann & Molina, 2009). Tapering rates should be individualized. Examples of benzodiazepine tapers and tips for managing benzodiazepine withdrawal are available (U.S. Department of Veterans Affairs and Department of Defense, 2015; Veterans Health Administration PBM Academic Detailing Service). CBT increases tapering success rates and might be particularly helpful for patients struggling with a benzodiazepine taper (Paquin, Zimmerman, & Rudolph, 2014). If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific anti-depressants or other nonbenzodiazepine medications approved for anxiety should be offered. 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 treatment with medication for patients with opioid use disorder (recommendation category: A, evidence type: 1).

Implementation considerations:

- *Although stigma can reduce the willingness of individuals with opioid use disorder to seek treatment, opioid use disorder is a chronic, treatable disease from which people can recover and continue to lead healthy lives*.
- *If clinicians suspect opioid use disorder, they should discuss their concern with their patient and provide an opportunity for the patient to disclose related concerns or problems.*
- *Clinicians should assess for the presence of opioid use disorder using DSM-5 criteria.*
- *For patients meeting criteria for opioid use disorder, particularly if moderate or severe, clinicians should offer or arrange for patients to receive treatment with medication for opioid use disorder.*
- *Clinicians should not dismiss patients from their practice because of opioid use disorder because this can adversely affect patient safety and could represent patient abandonment.*
- *Medication treatment of opioid use disorder has been associated with reduced overdose and overall mortality*. *Identification of opioid use disorder represents an opportunity for a clinician to initiate potentially life-saving interventions, and it is important for the clinician to collaborate with the patient regarding their safety to increase the likelihood of successful treatment.*
- *For pregnant people with opioid use disorder, medication therapy with buprenorphine or methadone has been associated with improved maternal outcomes and should be offered.*
- *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 buprenorphine or naltrexone treatment provider, or from an opioid treatment program certified by SAMHSA to provide methadone or buprenorphine for patients with opioid use disorder.*
- *All clinicians, and particularly clinicians prescribing opioids in communities without sufficient treatment capacity for opioid use disorder, should obtain a waiver to prescribe buprenorphine.*
- *Clinicians prescribing opioids should identify treatment resources for opioid use disorder in the community and should work together to ensure sufficient treatment capacity for opioid use disorder at the practice level.*

- *Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and opioid use disorder require ongoing pain management that maximizes benefits relative to risks.*

Supporting Rationale

Opioid use disorder (previously classified as opioid abuse or opioid dependence in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [DSM-IV] [American Psychiatric Association, 2000]) is defined in the DSM-5 as a "problematic pattern of opioid use leading to clinically significant impairment or distress." (American Psychiatric Association, 2013). Treatment with opioids for pain is associated with increased risk for opioid use disorder, particularly if opioids are prescribed for more than 90 days (Edlund et al., 2014). A systematic review found the rate of opioid "addiction" among chronic pain patients averaged between 8% and 12% in studies published between 2000 and 2013 (Vowles et al., 2015). More recently, studies have found prevalence estimates of 23.9% and 26.5% for any prescription opioid use disorder and 5.2% and 9.0% for moderate to severe opioid use disorder (using DSM-5 diagnostic criteria) among adults receiving long-term opioid therapy for pain, with slightly lower prevalence (21.5% for any and 4.2% for moderate to severe opioid use disorder) in clinics with more consistent use of risk reduction practices (Boscarino et al., 2020) (Von Korff et al., 2017).

Opioid use disorder is manifested by at least 2 out of 11 defined criteria occurring within a year (American Psychiatric Association, 2013):

(1) Taking opioids in larger amounts or over a longer period of time than intended

(2) Having a persistent desire or unsuccessful attempts to reduce or control opioid use

(3) Spending excess time obtaining, using or recovering from opioids

(4) Craving for opioids

(5) Continuing opioid use causing inability to fulfill work, home, or school responsibilities

(6) Continuing opioid use despite having persistent social or interpersonal problems

(7) Lack of involvement in social, occupational or recreational activities

(8) Using opioids in physically hazardous situations

(9) Continuing opioid use in spite of awareness of persistent physical or psychological problems

(10) Tolerance, as defined by either of the following:

a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect, or

b. Markedly diminished effect with continued use of the same amount of an opioid.

(11) Withdrawal, as manifested by either of the following:

a. The characteristic opioid withdrawal syndrome, or

b. Opioids (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.

Note: Criteria 10 and 11 are not considered to be met for those taking opioids solely under appropriate medical supervision (American Psychiatric Association, 2013).

Severity is specified as mild (2-3 criteria), moderate (4-5 criteria) or severe (≥6 criteria) (American Psychiatric Association, 2013).

FDA-approved medications indicated for the treatment of opioid use disorder and/or the prevention of relapse include buprenorphine, methadone, and naltrexone. The clinical evidence reviews found evidence on the effectiveness of interventions (e.g., medications, behavioral treatments) for opioid use disorder related to prescription opioids to be limited (Chou et al., April 2020). However, moderate quality evidence shows buprenorphine (a partial agonist opioid) and methadone (a full agonist opioid) to be effective in preventing relapse among patients with opioid use disorder involving heroin (Fullerton et al., 2014; Mattick, Breen, Kimber, & Davoli, 2009, 2014), though the presence of pain among patients in these studies is generally not described. In addition, a small number of studies have evaluated buprenorphine for patients with prescription opioid dependence (based on DSM-IV

(American Psychiatric Association, 2000) criteria) and found it effective in preventing relapse (Fiellin et al., 2014; Weiss et al., 2011). One study found that among people with opioid use disorder, prior prescription opioid use predicts stabilization on buprenorphine (Varisco, Shen, & Thornton, 2020). Another trial that performed buprenorphine induction and then randomized patients to buprenorphine taper versus maintenance was terminated early without reporting of planned outcomes because all patients randomized to the taper arm switched to maintenance or experienced a relapse; five of six patients in the maintenance arm completed the trial (Blondell et al., 2010). In another trial identified by the clinical evidence reviews, there was no difference between buprenorphine/naloxone and methadone in likelihood of retention in the study, pain, function, or self-reported side effects (Neumann et al., 2013). Buprenorphine and methadone treatment of opioid use disorder have been associated with reduced overdose mortality (Krawczyk et al., 2020) and reduced overall mortality (Pearce et al., 2020). Naltrexone (an opioid antagonist) can also be used for opioid use disorder, particularly for highly motivated persons (Krupitsky et al., 2011; Minozzi et al., 2011). Naltrexone blocks the effects of opioids if they are used. Naltrexone has not been evaluated in people with concomitant pain and opioid use disorder, and opioid medications for pain cannot be used in patients receiving naltrexone. Naltrexone requires adherence to daily oral therapy or monthly, long-acting injections. The effectiveness of oral naltrexone can be limited by poor medication adherence (Minozzi et al., 2011); oral naltrexone should not be used except under very limited circumstances (American Society of Addiction Medicine, 2020), e.g., for patients who would be able to comply with observed dosing to enhance adherence (American Psychiatric Association, 2013; American Society of Addiction Medicine, 2020). Naltrexone must also be started following full withdrawal from opioids, which is a challenge for some patients, but for patients who have already completed or are able to complete withdrawal, naltrexone has been found to have comparable effectiveness as buprenorphine in prevention of relapse (J. D. Lee et al., 2018).

Some studies suggest that using behavioral therapies in combination with medications for opioid use disorder can reduce opioid misuse and increase retention during treatment (Amato, Minozzi, Davoli, & Vecchi, 2011; Connock et al., 2007). At the same time, a study of treatment for prescription opioid dependence (based on DSM-IV (American Psychiatric Association, 2000) criteria) found opioid agonist treatment with buprenorphine and standard medical management (including basic counseling recommending abstinence and self-help group participation) as effective as buprenorphine combined with more intensive opioid dependence counseling (ODC: addiction, recovery, and relapse prevention education with self-help and lifestyle change recommendations, interactive exercises, and take-home assignments delivered by trained substance use treatment or mental health professionals in 45-60 minute sessions based on drug counseling manuals with demonstrated efficacy); neither standard medical management nor ODC alone, without buprenorphine, was effective in preventing relapse (Weiss et al., 2011). Current recommendations for treatment of opioid use disorder include that patients' psychosocial needs be assessed, and patients offered or referred to psychosocial treatment in collaboration with qualified behavioral healthcare providers based on individual patient needs, but that a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay medications for opioid use disorder (American Society of Addiction Medicine, 2020). Additional recommendations have been published on goals, components of, and types of effective psychosocial treatment to use in conjunction with pharmacological treatment of opioid use disorder (American Society of Addiction Medicine, 2020).

Experts agreed with the strength of the language in the recommendation statement, specifically with the word "should" and with recommendation category A, and some noted they thought the evidence type should be 1. Several experts thought opioid agonist/opioid partial agonist and opioid antagonist treatment should not be framed as equal options for opioid use disorder, noting that opioid

agonist and opioid partial agonist treatment have stronger evidence for better outcomes, does not require abstinence, have less challenges with inductions, and are much more widely utilized.

If clinicians suspect opioid use disorder based on patient concerns or behaviors or on findings in prescription drug monitoring program data (see Recommendation 9) or from toxicology testing (see Recommendation 10), they should discuss their concern with their patient and provide an opportunity for the patient to disclose related concerns or problems. Clinicians should assess for the presence of opioid use disorder using DSM-5 criteria (American Psychiatric Association, 2013). Opioid use disorder can co-exist with other substance use disorders, and patients who are actively using substances during opioid use disorder treatment might require greater support, potentially including involvement of an addiction specialist (American Society of Addiction Medicine, 2020). Clinicians should ask about use of alcohol and other substances (see Recommendation 8). Alternatively, clinicians can arrange for a substance use disorder treatment specialist to assess for the presence of opioid and other substance use disorders.

For patients meeting criteria for opioid use disorder, particularly if moderate or severe, clinicians should offer or arrange for patients to receive treatment with medication for opioid use disorder. Patients with opioid use disorder may benefit from counseling and referrals to mutual help groups such as Narcotics Anonymous (Substance Abuse and Mental Health Services Administration, 2021c). Clinicians should also offer naloxone and training on proper use for overdose reversal to patients with opioid use disorder and to their household members/significant others (American Society of Addiction Medicine, 2020) (see Recommendation 8). Clinicians should not dismiss patients from their practice because of opioid use disorder because this can adversely affect patient safety and could represent patient abandonment. Identification of opioid use disorder represents an opportunity for a clinician to initiate potentially life-saving interventions, and it is important for the clinician to collaborate with the patient regarding their safety to increase the likelihood of successful treatment. Detoxification

on its own, without medications for opioid use disorder, is not recommended for opioid use disorder due to increased risks of relapse, overdose, and overdose death (American Society of Addiction Medicine, 2020).

For pregnant people with opioid use disorder, medication therapy with buprenorphine or methadone has been associated with improved maternal outcomes and should be offered (see Recommendation 8 (Substance Abuse and Mental Health Services Administration, 2018a)). Transmucosal buprenophine (without naloxone) has been recommended during pregnancy to avoid potential prenatal exposure to naloxone, especially if injected, and evidence on the safety of naloxone in pregnant people remains limited (American Society of Addiction Medicine, 2020; The American College of Obstetricians and Gynecologists Committee on Obstetric Practice & American Society of Addiction Medicine, 2017). However, combination buprenorphine/naloxone products are frequently used, and experts have noted that combination products are likely to be safe and effective for pregnant individuals when taken as prescribed (American Society of Addiction Medicine, 2020; The American College of Obstetricians and Gynecologists Committee on Obstetric Practice & American Society of Addiction Medicine, 2017). The American College of Obstetricians and Gynecologists also recommends that if a woman is stable on naltrexone prior to pregnancy, the decision regarding whether to continue naltrexone treatment during pregnancy should involve a careful discussion between the provider and the patient, weighing the limited safety data on naltrexone with the potential risk of relapse with discontinuation of treatment (The American College of Obstetricians and Gynecologists Committee on Obstetric Practice & American Society of Addiction Medicine, 2017). The American Academy of Pediatrics recommends that for infants of mothers receiving buprenorphine or methadone for opioid use disorder who have not had relapse for ≥90 days, breastfeeding should be supported if there are no other contraindications (e.g., HIV infection) while for infants of women with active substance use or with relapses within the last 30 days, breastfeeding should be discouraged (Patrick et al., 2020).

To expand access to buprenorphine, in April 2021, the *Practice Guidelines for the Administration of Buprenorphine for Treating Opioid Use Disorder (U.S. Department of Health and Human Services, 2021)* exempted eligible physicians, physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives from previous Controlled Substances Act certification requirements related to training, counseling and other ancillary services (i.e., psychosocial services). To prescribe buprenorphine for opioid use disorder for up to 30 patients in an office-based setting, clinicians can now forgo or choose to undertake training but must still receive a waiver from SAMHSA. Information about qualifications and the process to obtain a waiver are available from SAMHSA (Substance Abuse and Mental Health Services Administration, 2021b).

Additional recommendations have been published previously on induction, use, and monitoring of buprenorphine treatment for opioid use disorder (American Society of Addiction Medicine, 2020; Substance Abuse and Mental Health Services Administration, 2021c). Buprenorphine for treatment of opioid use disorder is usually combined with naloxone in a sublingual or buccal film or tablet (e.g., Suboxone), to reduce the potential for misuse of buprenorphine when injected. Naloxone is not absorbed orally, but if buprenorphine/naloxone is manipulated and injected, naloxone can trigger opioid withdrawal (Indivior, 2017). Long-acting injectable formulations of buprenorphine became available in 2018 (U.S. Food and Drug Administration, 2020b). As a partial agonist, buprenorphine should generally not be initiated until there are objective signs of withdrawal, in order to avoid precipitating withdrawal. As an alternative for patients not yet in opioid withdrawal, some authors have described a low-dose induction approach (sometimes referred to as “microdosing”) (Randhawa, Brar, & Nolan, 2020; Robbins, Englander, & Gregg, 2021) to avoid precipitated withdrawal when initiating buprenorphine, although there is limited evidence to date regarding this approach. For standard (not low-dose) buprenorphine induction, once objective signs of withdrawal are observed, buprenorphine should be initiated, usually at a dose of 2 to 4 mg (American Society of Addiction Medicine, 2020) and titrated upwards under

supervision at approximately 2-hour intervals as needed to control withdrawal symptoms in 2 or 4 mg increments, up to 8 mg buprenorphine total over the first 24 hours (Indivior, 2017). On the second day, the patient can be given a single dose consisting of the total of the doses received the first day. If there are residual withdrawal symptoms, the dose may be increased in 4 mg increments, up to a maximum of 16 mg total in the 2nd 24 hours (Indivior, 2017). Protocols for initiating buprenorphine by patients at home following an initial encounter with a healthcare provider to establish the diagnosis of OUD and discuss medication therapy options are in use by more experienced clinicians (Joshua D. Lee, Vocci, & Fiellin, 2014). Most patients are maintained on 8 mg to 16 mg per day (Soeffing, Martin, Fingerhood, Jasinski, & Rastegar, 2009), with a range of 4 to 24 mg per day (Indivior, 2017); (American Society of Addiction Medicine, 2020) there is some evidence that suggests that 16 mg per day or more might be more effective than lower dosages (American Society of Addiction Medicine, 2020).

Importantly, opioid dosage thresholds for caution in the treatment of pain are not applicable to opioid agonist treatment of opioid use disorder (Houry, 2018) as recommended dosages of methadone and buprenorphine for opioid use disorder (American Society of Addiction Medicine, 2020) differ from those for pain management. There is no recommended duration limit for treatment of opioid use disorder with buprenorphine or methadone, and discontinuation is associated with risks for relapse and opioid overdose (American Society of Addiction Medicine, 2020). If discontinued, buprenorphine should be tapered very gradually (over several months) (American Society of Addiction Medicine, 2020).

Compared to buprenorphine, which can be prescribed by waivered clinicians in any setting or dispensed from a SAMHSA-certified opioid treatment program (OTP), ongoing methadone treatment for opioid use disorder can only be provided through an OTP. As short-term exceptions, any clinician can administer (but not prescribe) up to one day's supply of methadone or buprenorphine to treat acute opioid withdrawal per day for up to 3 days, while working to refer the patient to opioid use disorder treatment, and patients already receiving opioid use disorder treatment may continue to directly

receive methadone or buprenorphine treatment in an emergency department or in a hospital during inpatient hospitalization (U.S. Department of Justice Drug Enforcement Administration).

Naltrexone does not require a waiver and can be prescribed in any setting. Additional recommendations have been published previously on naltrexone treatment for opioid use disorder (American Society of Addiction Medicine, 2020). A minimum of 7 to 10 days free of opioids is recommended prior to the first naltrexone dose to avoid precipitation of severe opioid withdrawal (Alkermes, 2020). Extended-release injectable naltrexone is generally administered every 4 weeks by deep intramuscular (IM) injection in the gluteal muscle at 380 mg per injection (American Society of Addiction Medicine, 2020), alternating buttocks for each subsequent injection (Alkermes, 2020). Some patients, including those who metabolize naltrexone more rapidly, might benefit from dosing as frequently as every 3 weeks (American Society of Addiction Medicine, 2020). There is no recommended duration limit for treatment of opioid use disorder with naltrexone. If discontinued, naltrexone can be stopped abruptly without withdrawal symptoms (American Society of Addiction Medicine, 2020). Clinicians should warn patients who discontinue naltrexone of the risk of potentially fatal opioid overdose if opioid use is resumed (American Society of Addiction Medicine, 2020), due to the loss of tolerance to previous opioid dosage.

Clinicians are strongly encouraged to provide medication treatment for their patients with opioid use disorder. 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 buprenorphine or naltrexone treatment clinician, or from an opioid treatment program certified by SAMHSA to provide methadone or buprenorphine for patients with opioid use disorder. Resources to help with arranging for treatment include SAMHSA's buprenorphine physician locator (https://www.samhsa.gov/medication-assisted-treatment/practitioner-program-data/treatment-practitioner-locator) and SAMHSA's Opioid Treatment Program Directory

(https://dpt2.samhsa.gov/treatment/directory.aspx). Clinicians should assist patients in finding qualified treatment specialists and should arrange for patients to follow up with these specialists, as well as arranging for ongoing coordination of care. Treatment need in a community is often not met by capacity to provide buprenorphine or methadone therapy (Jones, Campopiano, Baldwin, & McCance-Katz, 2015). Clinicians prescribing opioids in communities without sufficient treatment capacity for opioid use disorder should obtain a waiver to prescribe buprenorphine. SAMHSA's Providers Clinical Support System (https://pcssnow.org/) offers training and technical assistance as well as mentors to assist clinicians in assessment for and the treatment of substance use disorders and specifically of opioid use disorder, and on the interface of pain and opioid misuse. Clinicians prescribing opioids should identify treatment resources for substance use disorders including opioid use disorders in the community and should work together to ensure sufficient treatment capacity at the practice level.

Management of opioid misuse that does not meet criteria for opioid use disorder

For patients with opioid misuse that does not meet criteria for opioid use disorder (e.g., taking opioids in larger amounts than intended without meeting other criteria for opioid use disorder), clinicians should reassess the patient's pain, ensure that therapies for pain management have been optimized (see Recommendation 2), discuss with patients, and carefully weigh benefits and risks of continuing opioids at the current dosage (see Recommendation 5). For patients who choose to but are unable to taper, clinicians may reassess for opioid use disorder and offer buprenorphine treatment or refer for buprenorphine or methadone treatment if criteria for opioid use disorder are met. Even without a diagnosis of opioid use disorder, transitioning to buprenorphine for pain can also be considered given reduced overdose risk with buprenorphine compared with risk associated with full agonist opioids (see Recommendation 5).

Pain management for patients with opioid use disorder

Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Clinicians should use nonpharmacologic and nonopioid pharmacologic pain treatments as appropriate (American Society of Addiction Medicine, 2020) (see Recommendations 1 and 2) to provide optimal pain management. For patients with pain who have an active opioid use disorder but are not in treatment, clinicians should consider buprenorphine or methadone treatment for opioid use disorder, which can also help with concurrent management of pain (American Society of Addiction Medicine, 2020). For patients who are treated with buprenorphine for opioid use disorder and experience acute pain, clinicians can consider temporarily increasing the buprenorphine dosing frequency (e.g., to twice a day (American Society of Addiction Medicine, 2020)) to help manage pain, given the duration of effects of buprenorphine is shorter for pain than for suppression of withdrawal (Alford et al., 2006). For severe acute pain (e.g., trauma and/or unplanned major surgery), clinicians can consider additional as-needed doses of buprenorphine for patients receiving buprenorphine for opioid use disorder and short-term use of higher-potency nonopioid analgesics (e.g., NSAIDs) for patients receiving naltrexone for opioid use disorder; patients receiving methadone for opioid use disorder who require additional opioids as treatment for pain management should be carefully monitored, and when feasible should optimally be treated by a clinician experienced in the treatment of pain in consultation with their opioid treatment program. (American Society of Addiction Medicine, 2020). The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder (2020 Focused Update) provides additional recommendations (see Part 9) (American Society of Addiction Medicine, 2020) for the management of patients receiving medications for opioid use disorder who have planned surgeries for which nonopioid therapies are not anticipated to provide sufficient pain relief.

Conclusions and future directions

CDC indicated the intent to evaluate and reassess the 2016 CDC guideline as new evidence became available and to determine when the closure of research gaps would prompt an update. To achieve these aims, CDC funded the AHRQ to conduct systematic reviews of the scientific evidence in the following five areas: noninvasive nonpharmacological treatments for chronic pain; nonopioid pharmacologic treatments for chronic pain; opioid treatments for chronic pain; treatments for acute pain; and acute treatments for episodic migraine (Chou et al., April 2020; Chou et al., December 2020; Halker Singh et al., December 2020; McDonagh et al., April 2020; Skelly et al., April 2020). Based upon these reviews, an update to the CDC 2016 Guideline was warranted.

The evidence reviews that informed this clinical practice guideline affirmed the appropriateness of the recommendations included in the 2016 CDC guideline for using opioids to treat chronic pain. The reviews also allowed CDC to expand the focus to include acute and subacute pain more explicitly. This clinical practice guideline also includes a new topline recommendation for patients with chronic pain who are already on higher opioid dosages. Specifically, the clinical practice guideline outlines how clinicians and patients should work together in assessing the benefits and risks of continued opioid use and if or when to taper opioids to a lower dosage or discontinue opioids all together in accordance with the HHS Tapering Guide (Dowell, Compton, & Giroir, 2019; U.S. Department of Health and Human Services, 2019a).

There are 4 key domains covered by the updated clinical practice guideline for prescribing of opioid pain medication for patients 18 and older for pain outside of sickle cell disease-related pain management, cancer pain treatment, palliative care, and end-of-life care. These include whether to initiate opioids for pain treatment; opioid selection and dosage; opioid duration and follow-up; and assessing the risks and addressing harms of opioid use. In addition, five guiding principles were

identified to inform implementation across recommendations that focus on the appropriate treatment of pain, flexibility to meet the care needs and clinical circumstances of each patient through a multimodal and multidisciplinary approach to pain management, avoiding misapplying the clinical practice guideline beyond its intended use, and vigilantly attending to health inequities and ensuring access to an appropriate, affordable, diversified, coordinated, and effective nonpharmacologic and pharmacologic pain treatment for all persons.

A central tenet of this clinical practice guideline is that acute, subacute, and chronic pain needs to be appropriately and effectively treated independent of whether opioids are part of a treatment regimen. This is done by selecting one or more nonpharmacologic or pharmacologic treatment modalities that maximize patient safety and optimize outcomes in pain, function, and quality of life. A multimodal and multidisciplinary approach to pain management attending to the biological, psychological, and social characteristics of each person is critical (U.S. Department of Health and Human Services, 2019b). The care provided needs to be individualized and person-centered (U.S. Department of Health and Human Services, 2019b). Clinicians and patients should work together to identify treatment goals and tailor an approach that considers both the benefits and risks of available options (U.S. Department of Health and Human Services, 2019b). Progress should be monitored over time and treatment protocols adjusted accordingly. Health systems and payers should work to ensure multimodal treatment options are available, accessible, and reimbursed for patients. Public and private payers should support a broader array of nonpharmacologic interventions such as exercise, multidisciplinary rehabilitation, mind-body interventions, cognitive behavioral therapy, and some complementary and integrative medicine therapies like acupuncture and spinal manipulation, given their increasingly known effectiveness (Skelly et al., April 2020). Reimbursement is often cited as a principle barrier to why these nonpharmacologic treatments are not more widely used (Skelly et al., April 2020).

An integral part of providing access to and delivery of high-quality healthcare, including pain treatment, is understanding how the social determinants of health influence the healthcare provided and the differential outcomes observed (Agency for Healthcare Research and Quality, 2020). Social, economic, educational, and neighborhood-level factors may create and exacerbate health inequities experienced across the life course (Agency for Healthcare Research and Quality, 2020). These social determinants of health are borne out of historical and contemporary injustices that advantage some and disadvantage others in society leading to the systemic marginalization or oppression of some groups such as people from some racial and ethnic groups, people living in rural areas, persons experiencing homelessness, people with disabilities, people with substance use disorders, justice-involved populations, and non-US born persons among others (Centers for Disease Control and Prevention, 2020a).

Outcomes are also influenced by the healthcare context (Agency for Healthcare Research and Quality, 2020). Differential access to and coverage for high-quality, culturally and linguistically appropriate, health-literate care may influence attitudes towards healthcare and use of available services (Agency for Healthcare Research and Quality, 2020). Prejudice, bias, discrimination, and stereotyping by individual clinicians, practices, health systems, and payers serve to reinforce these health disparities (Institute of Medicine, 2003). Clinicians, practices, health systems, and payers should attend to health inequities to ensure access to appropriate, diversified, effective nonpharmacologic and pharmacologic pain management options that are person-centered, affordable, accessible, and well-coordinated as well as protect patient safety and guard against unnecessary risks. This begins with raising awareness and acknowledging the presence of these inequities, strengthening patient-clinician communication, leveraging community health workers, implementing multidisciplinary care teams, tracking and monitoring performance measures, and integrating quality improvement initiatives that support and invest in guideline concordant care for all persons (Institute of Medicine, 2003).

Special attention should be given to avoid misapplying this updated clinical practice guideline beyond its intended use or implementing policies purportedly derived from it that result in unintended consequences for patients (Dowell, Haegerich, et al., 2019). This includes being inflexible on opioid dose and duration, discontinuing or dismissing patients from a practice, rapidly and non-collaboratively tapering patients who may be stable on a higher dose, and applying recommendations to populations that are not a focus of the clinical practice guideline such as patients with cancer, sickle cell disease, or during end-of-life care (Dowell, Haegerich, et al., 2019).

The uptake and widespread utilization of the 2016 CDC guideline hinged on its successful dissemination. CDC invested in activities to support its translation and integration into clinical practice. Most notably, CDC produced a checklist and mobile app for clinicians to more readily follow guideline recommendations; fact sheets, posters, and public service announcements (PSAs) making key components of the guideline more accessible and understandable to clinicians and patients; and a 14-module interactive, web-based training featuring self-paced learning, case-based content, knowledge checks, and integrated resources for clinicians (Centers for Disease Control and Prevention, 2021b). CDC also developed and implemented a quality improvement (QI) and care coordination initiative to improve and encourage careful and selective use of long-term opioid therapy in the context of managing chronic pain (Centers for Disease Control and Prevention, 2018b). This included 16 clinical quality improvement measures (Shoemaker-Hunt et al., 2021) as well as practice-level strategies to help health systems organize and improve the management and coordination of opioid therapy using an interdisciplinary team approach, establishing practice policies and standards, and leveraging EHR data to develop registries and track QI measures (Centers for Disease Control and Prevention, 2018b). CDC invested in health IT and other clinical decision support tools by collaborating with the Office of the National Coordinator for Health Information Technology (ONC) to create and integrate guideline-concordant care into clinical workflow (Centers for Disease Control and Prevention, 2021b). In addition, CDC compiled

complementary clinical recommendations from professional organizations for clinicians to reference for several common conditions associated with acute pain – including acute migraines, ankle sprains, dental pain, acute low back pain, and post-surgical pain (Centers for Disease Control and Prevention, 2020b). All information in the web-based resource is based on external research (Mikosz et al., 2020) and existing published guidelines from professional organizations. The compilation can further assist clinicians and patients, working together, in making safer and more effective pain management decisions.

This updated clinical practice guideline provides overarching voluntary recommendations on the use of opioids to treat pain. To assist in the uptake and understanding of this clinical practice guideline, CDC will update existing resources to align with the new clinical practice guideline and develop new tools and resources for clinicians, health systems, patients, and others on the use of opioid and non-opioid pain treatments — including resources supporting health equity. Finally, CDC will work with public and private payers with the aim of improving coverage for nonpharmacologic treatments, increasing access to non-opioid pain medication, supporting patient counseling and coordination of care, increasing access to evidence-based treatments of opioid use disorder, and enhancing availability of multidisciplinary and multimodal care. Robust coverage and access (e.g., limited utilization management and cost sharing for evidence-based treatments) and decision support (e.g., adjustment of EHR prescribing defaults) can be used to nudge clinicians and patients toward evidence-based treatments as default treatments for pain (Ancker et al., 2021; Montoy, Coralic, Herring, Clattenburg, & Raven, 2020).

This clinical practice guideline updates and expands upon the recommendations in the 2016 CDC Guideline and is based on the best available evidence as interpreted and informed by expert opinion and attending to the values and preferences of patients, caregivers, and clinicians. While clinical scientific evidence continues to advance and supports the recommendations in the clinical practice guideline, the

strength of the evidence is sometimes weak and research gaps remain (Chou et al., April 2020; Chou et al., December 2020; Halker Singh et al., December 2020; McDonagh et al., April 2020; National Academies of Sciences Engineering and Medicine, Health and Medicine Division, Board on Health Sciences Policy, & Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse, 2017; Skelly et al., April 2020; U.S. Department of Health and Human Services, 2019b).

The areas in need of additional research include but are not limited to

- Efficacy of screening tools to assess risk for opioid misuse and developing an opioid use disorder.
- Effective management of patients on high dose opioids; the application of multidisciplinary and multimodal models of pain treatment, and service delivery modalities including telehealth.
- Long-term comparative effectiveness of pharmacologic and nonpharmacologic therapies.
- Effects of therapies on non-pain outcomes.
- Treatment outcomes for specific pain conditions and how benefits and risks of therapies vary among sub-populations.
- Adapting evidence-based opioid prescribing and pain management strategies to meet the needs of special populations including people from some racial and ethnic groups, older adults, and rural communities.
- Improved diagnostics in measuring pain.

- Enhanced clinician and patient education about pain and the use of opioids; the assessment of practice-level strategies in health systems to improve management and care coordination for patients on opioid therapy.
- Transition from acute to chronic pain and how to apply effective diagnostic, preventive, and therapeutic approaches.
- Effect of stigma as a barrier for treating pain and getting treatment for an opioid use disorder.

In closing, the principle aim of this clinical practice guideline is to ensure people have access to safe, accessible, and effective pain management that improves their function and quality of life while illuminating and reducing risks associated with prescription opioids, and ultimately reducing the consequences of prescription opioid misuse and overdose. Lessons learned from the development of the 2016 CDC guideline informed the process used to generate this update. CDC will evaluate the clinical practice guideline to identify the impact of the recommendations on clinician and patient outcomes as well as the intended and unintended consequences. Communication between clinicians and patients about the risks and benefits of opioids should be central to treatment decisions for patients in pain. This clinical practice guideline can help inform those decisions and assist clinicians in meeting the unique needs of each person. CDC will revisit this clinical practice guideline when remaining evidence gaps have sufficiently been addressed and another update is warranted.

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Note: Formatting is currently based on automatic EndNote settings and will be adjusted (e.g., changing to numbered in-text citations).

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TABLE. Morphine milligram equivalent (MME) doses for commonly prescribed opioids for pain management

Opioid	Conversion factor*
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	5
Methadone	4.7
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Tapentadol[†]	0.4
Tramadol[¥]	0.2

Source: Adapted from Von Korff M, Saunders K, Ray GT, et al. Clin J Pain 2008;24:521–7; Nielsen S, Degenhardt L, Hoban B, Gisev N. Pharmacoepidemiol Drug Saf. 2016;25(6):733-737.

*Multiply the dose for each opioid by the conversion factor to determine the dose in MMEs. For example, tablets containing hydrocodone 5 mg and acetaminophen 325 mg taken four times a day would contain a total of 20 mg of hydrocodone daily, equivalent to 20 MME daily; extended-release tablets containing oxycodone 10mg and taken twice a day would contain a total of 20mg of oxycodone daily, equivalent to 30 MME daily.
The following cautions should be noted: 1) All doses are in mg/day except for fentanyl, which is mcg/hr. 2) Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics. 3) Do not use the calculated dose in MMEs to determine the doses to use when converting one opioid to another; when converting opioids, the new opioid is typically dosed at a substantially lower dose than the calculated MME dose to avoid overdose due to incomplete cross-tolerance and individual variability in opioid pharmacokinetics. 4) Use particular caution with methadone dose conversions because methadone has a long and variable half-life, and peak respiratory depressant effect occurs later and lasts longer than peak analgesic effect. 5) Use particular caution with transdermal fentanyl since it is dosed in mcg/hr instead of mg/day, and its absorption is affected by heat and other factors. 6) Buprenorphine products approved for the treatment of pain are not included in the table due to their partial mu receptor agonist activity and resultant ceiling effects compared to full mu receptor agonists. 7) These conversion factors should not be applied to dosage decisions related to the management of opioid use disorder.

[†]Tapentadol is a mu receptor agonist and norepinephrine reuptake inhibitor. MMEs are based on degree of mu-receptor agonist activity, but it is unknown if tapentadol is associated with overdose in the same dose-dependent manner as observed with medications that are solely mu receptor agonists.

[¥]Tramadol is a mu receptor agonist and norepinephrine and serotonin reuptake inhibitor. MMEs are based on degree of mu-receptor agonist activity, but it is unknown if tramadol is associated with overdose in the same dose-dependent manner as observed with medications that are solely mu receptor agonists.

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Ex-Officio Members: Melissa L. Brodowski, PhD, MSW, MPH; Dawn Castillo, MPH; Mindy J. D. Chai, PhD; Wilson Compton, MD, MPH; CAPT Jennifer Fan, PhD; Meredith A. Fox, PhD; Holly Hedegaard, MD, MSPH; John Howard, MD; Lyndon J. O. Joseph, PhD; Valerie Maholmes, PhD, CAS; Bethany D. Miller, LSCW-C, MEd; Constantinos Miskis, JD; Judy A. Staffa, PhD, RPh; RADM Kelly M. Taylor, MS, REHS

Disclosure of relationship

The Opioid Workgroup members disclose that they have no financial conflicts of interest. Members disclose the following activities related to the content of this clinical practice guideline: Anne L. Burns discloses that she is employed by the American Pharmacists Association, a nonprofit 501c6 organization, where she is involved in advancing pharmacists' patient care services, including pain management services, and she serves on the Board of Directors for the Pharmacy Quality Alliance, a nonprofit organization that develops quality measures, including opioid-related measures. Beth Darnall discloses that she consulted with AppliedVR, a virtual reality for chronic and acute pain company. Neeraj Gandotra discloses that he provided expert testimony before the Senate Judiciary Committee on 12/17/2019 on behalf of SAMHSA regarding the opioid epidemic. Christine Goertz discloses that she served as a consultant to the American Chiropractic Association until September 30, 2019, and that she has NIH foundation funding to conduct research on non-pharmacologic approaches to pain management. Jennifer Waljee discloses that she received research support funding from the Centers for Disease Control and Prevention, National Institutes of Health, Michigan Department of Health and Human Services, and the Substance Abuse and Mental Health Administration for research examining the effect of opioid use prior to and after surgery on postoperative outcomes.

The Board of Scientific Counselors of the National Center for Injury Prevention and Control (BSC/NCIPC) members disclose that they have no financial conflicts of interest. Three BSC/NCIPC members, Chinazo O. Cunningham, Frank Floyd, and Elizabeth Habermann, served on the Opioid Workgroup. Roger Chou is a co-author of the clinical practice guideline and AHRQ- sponsored systematic clinical evidence reviews. Dr. Chou disclosed that he receives funding to conduct reviews on opioids and recused himself from the July 16, 2021, BSC/NCIPC meeting and discussion of the OWG report on the draft clinical practice guideline. Wilson Compton discloses that he has long-term stock holdings in

General Electric, Pfizer, and 3M Companies; however, his investments in these companies did not exceed the U.S. Department of Health and Human Services threshold for significant financial interest.

BOX 1. CDC recommendations for prescribing opioids for outpatients with pain outside of sickle cell disease-related pain management, cancer pain treatment, palliative care, and end-of-life care

Determining whether or not to initiate opioids for pain

1. Nonopioid therapies are effective for many common types of acute pain. Clinicians should only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient. (recommendation category: B, evidence type: 3).

2. Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks (recommendation category: A, evidence type: 2).

Opioid selection and dosage

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

4. When opioids are started for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest dosage to achieve expected effects. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients (recommendation category: A, evidence type: 3).

5. For patients already receiving higher opioid dosages, clinicians should carefully weigh benefits and risks and exercise care when reducing or continuing opioid dosage. If risks outweigh benefits of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to lower dosages or, if warranted based on the individual clinical circumstances of the patient, to appropriately taper and discontinue opioids. Unless there are indications of a life-threatening issue, such as warning signs of impending overdose, e.g., confusion, sedation, or slurred speech, opioid therapy should not be discontinued abruptly, and clinicians should not abruptly or rapidly reduce opioid dosages from higher dosages (recommendation category: B, evidence type: 4).

Opioid duration and follow-up

6. When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids (recommendation category: A, evidence type: 4).

7. Clinicians should evaluate benefits and risks with patients within 1 to 4 weeks of starting opioid therapy for subacute or chronic pain or of dose escalation. Clinicians should evaluate benefits and

risks of continued therapy with patients every 3 months or more frequently (recommendation category: B, evidence type: 4).

Assessing risk and addressing harms of opioid use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone when factors that increase risk for opioid overdose are present (recommendation category: A, evidence type: 4).

9. When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, 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 combinations that put the patient at high risk for overdose (recommendation category: B, evidence type: 4).

10. When prescribing opioids for subacute or chronic pain, clinicians should consider toxicology testing to assess for prescribed medications as well as other prescribed and non-prescribed controlled substances (recommendation category: B, evidence type: 4).

11. Clinicians should use extreme caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants (recommendation category: B, evidence type: 3).

12. Clinicians should offer or arrange treatment with medication for patients with opioid use disorder (recommendation category: A, evidence type: 1).

* See full clinical practice guideline for recommendation categories and evidence ratings.

These five guiding principles should broadly inform implementation across recommendations:

1. Acute, subacute, and chronic pain need to be appropriately and effectively treated independent of whether opioids are part of a treatment regimen.

2. Recommendations are voluntary and are intended to support, not supplant, individualized, person-centered care. Flexibility to meet the care needs and the clinical circumstances of a specific patient are paramount.

3. A multimodal and multidisciplinary approach to pain management attending to the physical health, behavioral health, long-term services and supports, and expected health outcomes and well-being needs of each person is critical.

4. Special attention should be given to avoid misapplying this updated clinical practice guideline beyond its intended use or implementing policies purportedly derived from it that might lead to unintended consequences for patients.

5. Clinicians, practices, health systems, and payers should vigilantly attend to health inequities, provide culturally and linguistically appropriate communication, and ensure access to an

appropriate, affordable, diversified, coordinated, and effective nonpharmacologic and pharmacologic pain management regimen for all persons.

BOX 2. Interpretation of recommendation categories and evidence type

Recommendation categories

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

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

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

Evidence type

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

Type 1 evidence: Randomized 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.