EXHIBIT
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CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022

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Summary

This guideline provides recommendations for clinicians providing pain care, including those prescribing opioids, for outpatients aged ≥18 years. It updates the CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016 (MMWR Recomm Rep 2016;65[No. RR-1]:1–49) *and includes recommendations for managing acute (duration of <1 month), subacute (duration of 1–3 months), and chronic (duration of >3 months) pain. The recommendations do not apply to pain related to sickle cell disease or cancer or to patients receiving palliative or end-of-life care. The guideline addresses the following four areas: 1) determining whether or not to initiate opioids for pain, 2) selecting opioids and determining opioid dosages, 3) deciding duration of initial opioid prescription and conducting follow-up, and 4) assessing risk and addressing potential harms of opioid use. CDC developed the guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Recommendations are based on systematic reviews of the scientific evidence and reflect considerations of benefits and harms, patient and clinician values and preferences, and resource allocation. CDC obtained input from the Board of Scientific Counselors of the National Center for Injury Prevention and Control (a federally chartered advisory committee), the public, and peer reviewers. CDC recommends that persons with pain receive appropriate pain treatment, with careful consideration of the benefits and risks of all treatment options in the context of the patient's circumstances. Recommendations should not be applied as inflexible standards of care across patient populations. This clinical practice guideline is intended to improve communication between clinicians and patients about the benefits and risks of pain treatments, including opioid therapy; improve the effectiveness and safety of pain treatment; mitigate pain; improve function and quality of life for patients with pain; and reduce risks associated with opioid pain therapy, including opioid use disorder, overdose, and death.*

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Introduction

Background

Pain is one of the most common reasons adults seek medical care in the United States (*1*). Acute pain, a nearly universal experience, is a physiologic response to noxious stimuli that can become pathologic. Acute pain is usually sudden in onset and time limited (defined in this clinical practice guideline as having a duration of <1 month) and often is caused by injury, trauma, or medical treatments such as surgery (*2,3*). Unresolved acute pain or subacute pain (defined in this clinical practice guideline as pain that has been present for 1–3 months) can evolve into chronic pain (*4*). Chronic pain typically lasts >3 months (*4*) and can be the result of an underlying medical disease or condition, injury, medical treatment, inflammation, or unknown cause (*2*). Approximately one in five U.S. adults had chronic pain in 2019 and approximately one in 14 adults experienced "high-impact" chronic pain, defined as having pain on most days or every day during the past 3 months that limited life or work activities (*5*). Pain, especially chronic pain, can affect almost every aspect of a person's life, leading to impaired physical functioning, poor mental health, and reduced quality of life, and contributes to substantial morbidity each year (*6*). 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 (*2*).

Pain is a complex phenomenon influenced by multiple factors, including biologic, psychological, and social factors (*7*). This complexity means substantial heterogeneity exists in the effectiveness of various pain treatments, depending on the type of underlying pain or condition being treated (*7–11*). Patients might experience persistent pain that is not well controlled (*6*). Chronic pain often co-occurs with behavioral health conditions, including mental and substance use disorders (*12,13*). Patients with chronic pain also are at increased risk for suicidal ideation and behaviors (*14,15*). Data from death investigations in 18 states during 2003–2014 indicate that approximately 9% of suicide decedents had evidence of having chronic pain at the time of death; however, this is likely an underestimate because of the limitations of the underlying data sources used in the study (*16*). These factors and potentially harmful outcomes associated with chronic pain for some persons add to the clinical complexity and underscore the importance of adequately treating and providing care to persons with pain. Thus, prevention, assessment, and treatment of pain is a persistent challenge for clinicians. Pain might go unrecognized, and some persons (e.g., members of marginalized racial and ethnic groups; women; older persons; persons with cognitive impairment; persons with mental and substance use disorders, sickle cell disease, or cancer-related pain; and persons at the end of life) can be at risk for inadequate pain treatment (*2,6,17–23*).

Although substantial opportunity exists for improved pain management broadly across the United States, data underscore opportunities for addressing specific, long-standing health disparities (*24–26*) in the treatment of pain. For example, patients who identify as Black or African American (Black), Hispanic or Latino (Hispanic), and Asian receive fewer postpartum pain assessments relative to White patients (*27*). Black (*28,29*) and Hispanic (*29*) patients are less likely than White patients 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 Black patients receive prescription opioids at lower dosages than White patients (*24,30*). Racial and ethnic differences remain even after adjusting for access-related factors, the needs and preferences of patients, and the appropriateness of the intervention (*25*). These disparities appear to be further magnified for Black and Hispanic patients who live in socioeconomically disadvantaged neighborhoods (*26*). Women might be at higher risk for inadequate pain management (*31*), although they have higher opioid prescription fill rates (*32*) than men at a population level. Geographic disparities contribute to increased use of opioids for conditions for which nonopioid treatment options might be preferred but are less available. For example, adults living in rural areas are more likely to be prescribed opioids for chronic nonmalignant pain than adults living in nonrural areas (*33*). Although not Hispanic or Latino (non-Hispanic) American Indian or Alaska Native and non-Hispanic White populations have experienced much higher rates of prescription opioid–related overdose deaths than non-Hispanic Black, Hispanic, or non-Hispanic Asian or Pacific Islander populations (*34*), application of safeguards in opioid prescribing are disproportionately applied to Black patients. In one study, Black patients were more likely than White patients to receive regular office visits and have restricted early refills (*35*). In another study, clinicians were substantially more likely to discontinue opioids if there was evidence of misuse for Black patients compared with White patients (*36*). Differentially untreated or undertreated pain as a result of clinician biases persists and demands immediate and sustained attention and action (*37–40*).

Because of 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 (*2,6*). An important aim of pain management is the provision of person-centered care built on trust between patients and clinicians. Such care includes appropriate evaluation to identify potentially reversible causes of pain and establish a diagnosis and measurable treatment outcomes that focus on optimizing function and quality of life (*6*). To achieve this aim, it is important that clinicians consider the full range of pharmacologic and nonpharmacologic treatments for pain care, and that 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 has historically been inaccessible to many patients because of factors such as 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 about the evidence supporting different pain treatments (*6,17,41–46*). Partly because of 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; most placebo-controlled trials have been <6 weeks in duration (*2,6,47,48*).

Opioids can be essential medications for the management of pain; however, they carry considerable 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 long-term prescription opioid use was found to be associated with increased risk for overdose and opioid misuse, among other risks (*47*). Some risks, such as overdose, were dose dependent (*47*). In 2014, on the basis of accumulating evidence of potential risks to patients, the Food and Drug Administration (FDA) required new safety labeling changes for extended-release and long-acting opioids. Changes included a boxed warning on the "risks of addiction, abuse, and misuse, which can lead to overdose and death" and, for patients receiving opioids during pregnancy, the risk for neonatal abstinence syndrome (a group of conditions that can occur when newborns withdraw from certain substances including opioids; withdrawal caused by in utero exposure to opioids also is called neonatal opioid withdrawal syndrome) (*49*). In 2016, these warnings were added to the labels for immediate-release opioids (*50*).

In addition to the potential risks to patients, prescribed opioids have the potential for diversion and nonmedical use among persons to whom they were not prescribed (*51*). In the United States, opioid prescribing increased fourfold during 1999–2010; this increase was paralleled by an approximately fourfold increase in overdose deaths involving prescription opioids during the same period (*52*) and increases in prescription opioid use disorder (*53*). In addition to the increased overall volume of opioid prescriptions during this period, how opioids were prescribed also changed; opioids increasingly were prescribed at higher dosages and for longer durations, prescribing behaviors associated with opioid use disorder and overdose (*54,55*). The limited evidence of long-term effectiveness of opioids for chronic pain, coupled with risks to patients and to persons using prescription opioids that were not prescribed to them, underscored the importance of reducing inappropriate opioid prescribing while advancing evidence-based pain care to improve the lives of persons living with pain.

CDC recognized the need for a national guideline on pain management that could improve appropriate opioid prescribing while minimizing opioid-related risks and released the *CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016* (referred to as the 2016 CDC Opioid Prescribing Guideline hereafter). The 2016 CDC Opioid Prescribing Guideline included 12 recommendations for the prescribing of opioids for chronic pain by primary care clinicians in outpatient settings, excluding active cancer treatment, palliative care, and end-of-life care (*56*). The recommendations in the 2016 CDC Opioid Prescribing Guideline were based on a systematic review of the best-available evidence at the time, along with input from experts and the public and review and deliberation by the Board of Scientific Counselors (BSC) of the National Center for Injury Prevention and Control (NCIPC) (a federally chartered advisory committee). The goals of the guideline were to 1) 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, experienced overdose, or experienced other prescription opioid–related adverse events (*56*). To facilitate uptake and implementation of the 2016 CDC Opioid Prescribing Guideline in clinical practice, CDC used a broad-reaching strategy that included clinician education and training, partnerships with health systems and payers, and multiple clinical tools and fact sheets (*57*).

The number of overall opioid prescriptions in the United States declined after 2012, and further declines have been observed after the release of the 2016 CDC Opioid Prescribing Guideline (*58*). The timing of this release was associated with accelerated decreases in overall opioid prescribing and declines in potentially high-risk prescribing (e.g., high-dosage opioid prescribing and concurrent prescribing of opioid pain medication and benzodiazepines) (*58,59*). The release of the 2016 CDC Opioid Prescribing Guideline also was temporally associated with modest increases in the prescribing of nonopioid pain medication (*60*). Although not the intent of the 2016 CDC Opioid Prescribing Guideline, design and implementation of new laws, regulations, and policies also appeared to reflect its recommendations. For example, since 2016, consistent with SUPPORT Act requirements (*61*), some state Medicaid programs have used the guideline and other resources to promote nonopioid options for chronic pain management (*62*). Approximately half of all states have passed legislation limiting initial opioid prescriptions for acute pain to a ≤7-day supply (*63*), and many insurers, pharmacy benefit managers, and pharmacies have enacted similar policies (*64*). At least 17 states have passed laws requiring or recommending the coprescription of naloxone in the presence of overdose risk factors, such as high dosages of opioids or concomitant opioid pain medications and benzodiazepines (*65*).

Although some laws, regulations, and policies that appear to support recommendations in the 2016 CDC Opioid Prescribing Guideline might have had positive results for some patients, they are inconsistent with a central tenet of the guideline: that the recommendations are voluntary and intended to be flexible to support, not supplant, individualized, patient-centered care. Of particular concern, some policies purportedly drawn from the 2016 CDC Opioid Prescribing Guideline have been notably inconsistent with it and have gone well beyond its clinical recommendations (*6,66,67*). Such misapplication includes extension to patient populations not covered in the 2016 CDC Opioid Prescribing Guideline (e.g., cancer and palliative care patients), rapid 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 pharmacies, and patient dismissal and abandonment (*66–68*). These actions are not consistent with the 2016 CDC Opioid Prescribing 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 (*66–71*).

Rationale

Since release of the 2016 CDC Opioid Prescribing Guideline, new evidence has emerged on the benefits and risks of prescription opioids for both acute and chronic pain, comparisons with nonopioid pain treatments, dosing strategies, opioid dose-dependent effects, risk mitigation strategies, and opioid tapering and discontinuation (*7–11*). This evidence includes studies on misapplication of the 2016 CDC Opioid Prescribing Guideline (*66*), benefits and risks of different tapering strategies and rapid tapering associated with patient harm (*68,71–73*), challenges in patient access to opioids (*6*), patient abandonment and abrupt discontinuation of opioids (*71*), a seminal randomized clinical trial comparing prescription opioids to nonopioid medications on long-term pain outcomes (*74*), the association of characteristics of initial opioid prescriptions with subsequent likelihood for long-term opioid use (*75,76*), and the small proportion of opioids used by patients compared with the amount prescribed to them for postoperative pain (*77–79*).

Opioid medications remain a common treatment for pain despite declines in the number of opioid prescriptions after 2012 (*58*). During 2015–2018, approximately 6% of U.S. adults reported use of one or more prescription opioids during the past 30 days (*80*), and in 2020, approximately 143 million opioid prescriptions were dispensed from pharmacies in the United States (*81*). 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 often are discordant with the 2016 CDC Opioid Prescribing Guideline recommendations (*25,77,82–84*). The prevalence of prescription opioid misuse and prescription opioid use disorder also has declined in recent years. In 2019, among persons aged ≥12 years in the United States, 9.7 million reported misuse of prescription opioids during the past year (a decrease from 12.5 million in 2015), and 1.4 million met criteria for a past-year prescription opioid use disorder (a decrease from 2.0 million in 2015) (*85*). However, in 2020, prescription opioids remained the most commonly misused prescription drug in the United States (*51*). Also in 2020, among those reporting misuse during the past year, 64.6% reported the main reason for their most recent misuse was to "relieve physical pain" compared with 11.3% to "feel good or get high" and 2.3% "because I am hooked or have to have it" (*51*). Taken together, these factors underscore the need for an updated clinical practice guideline on appropriate opioid prescribing for pain and pain management.

This clinical practice guideline expands and updates the 2016 CDC Opioid Prescribing Guideline to provide evidence-based recommendations for prescribing opioid pain medication for acute, subacute, and chronic pain for outpatients aged ≥18 years, excluding pain management related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care (Boxes 1 and 2). Lessons learned from the development of the 2016 CDC Opioid Prescribing Guideline informed the process used to generate this update. This 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 patients who have been receiving opioids as part of their ongoing pain management.

CDC developed a draft clinical practice guideline on the basis of five systematic reviews of the best-available evidence on the benefits and risks of prescription opioids, nonopioid pharmacologic treatments, and nonpharmacologic treatments. The draft clinical practice guideline was reviewed by an independent federal advisory committee (the Board of Scientific Counselors of the National Center for Injury Prevention and Control), peer reviewers, and the public and was revised after feedback from these reviews. Additional insights from patients, caregivers, and clinicians shared during virtual conversations held in 2020 were incorporated in the update. Importantly, to discourage the misapplication of opioid pain medication dosage thresholds as inflexible standards, revised recommendation statement language emphasizes principles such as avoiding increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients. More-specific considerations related to dosage have been moved to implementation considerations that follow each recommendation statement, where more nuance is offered to inform clinical decision-making and individualized patient care.

This clinical practice guideline provides recommendations but 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; thus, they should be considered in the context of the clinician-patient relationship built on 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 patient-centered clinical treatment decisions. The recommendations aim to improve communication between clinicians and patients about the benefits and risks of prescription opioids and other pain treatment strategies; improve the safety and effectiveness of pain treatment; improve pain, function, and quality of life for persons with pain; and reduce the risks associated with opioid pain treatment (including opioid use disorder, overdose, and death) and with other pain treatment.

This clinical practice guideline provides voluntary clinical practice recommendations for clinicians that should not be used as inflexible standards of care. The recommendations are not intended to be implemented as absolute limits for policy or practice across populations by organizations, health care systems, or government entities.