# Regulatory Advisory Panel on Opioids and Buprenorphine

Virginia Board of Medicine

March 31, 2023

9:00 a.m.

# Regulatory Advisory Panel on Opioids and Buprenorphine

Board of Medicine
Friday, March 31, 2023 @ 9:00 a.m.
9960 Mayland Drive, Suite 201 – Board Room 2
Henrico, Virginia

Call to Order

Emergency Egress Procedures i

Roll Call

Panel Member Introductions

Public Comment on Agenda Items

**New Business:**

1. Charge of the Panel and Overview of the Packet ..... ii

2. Speakers:
   - Kathrin Hobron – Office of the Chief Medical Examiner
   - Ashley Carter – Prescription Monitoring Program
   - Justin Wood – Drug Enforcement Administration
   - Anthony McDowell – Opioid Abatement Authority

3. Section by Section Review and Discussion of the Regulations

4. Consensus on Recommended Changes

5. Next Steps

Announcements

Travel Reminder

Adjournment

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## Charge of the Regulatory Advisory Panel

In March of 2017, Governor McAuliffe signed emergency regulations for prescribing opioids for pain and buprenorphine for substance use disorder. 18VAC85-21-10 et seq became effective immediately upon his signing. The emergency regulations had to be replaced by final regulations which became effective in August of 2018. It is time for a review of the regulations given that more data and more literature on these topics now exist. The Panel will bring its expertise to this review, aided by the briefings to be heard today and the information in the agenda packet.

## Contents of the Agenda Packet

The Board's regulations, recent federal initiatives, a petition for rulemaking, articles on pain and addiction and comments received in advance are included for review prior to the meeting.

Virginia Administrative Code
Title 18. Professional And Occupational Licensing
Agency 85. Board of Medicine
Chapter 21. Regulations Governing Prescribing of Opioids and Buprenorphine

# Part I. General Provisions

## 18VAC85-21-10. Applicability.

A. This chapter shall apply to doctors of medicine, osteopathic medicine, and podiatry and to physician assistants.

B. This chapter shall not apply to:

1. The treatment of acute or chronic pain related to (i) cancer, (ii) sickle cell, (iii) a patient in hospice care, or (iv) a patient in palliative care;

2. The treatment of acute or chronic pain during an inpatient hospital admission or in a nursing home or an assisted living facility that uses a sole source pharmacy; or

3. A patient enrolled in a clinical trial as authorized by state or federal law.

**Statutory Authority**
§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

**Historical Notes**
Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-20. Definitions.

The following words and terms when used in this chapter shall have the following meanings unless the context clearly indicates otherwise:

"Acute pain" means pain that occurs within the normal course of a disease or condition or as the result of surgery for which controlled substances may be prescribed for no more than three months.

"Board" means the Virginia Board of Medicine.

"Chronic pain" means nonmalignant pain that goes beyond the normal course of a disease or condition for which controlled substances may be prescribed for a period greater than three months.

"Controlled substance" means drugs listed in The Drug Control Act (§ 54.1-3400 et seq. of the Code of Virginia) in Schedules II through IV.

"FDA" means the U.S. Food and Drug Administration.

"MME" means morphine milligram equivalent.

"Prescription Monitoring Program" means the electronic system within the Department of Health

Professions that monitors the dispensing of certain controlled substances.

"SAMHSA" means the federal Substance Abuse and Mental Health Services Administration.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-21. Electronic prescribing.

A. Beginning July 1, 2020, a prescription for a controlled substance that contains an opioid shall be issued as an electronic prescription consistent with § 54.1-3408.02 of the Code of Virginia, unless the prescription qualifies for an exemption as set forth in subsection C of § 54.1-3408.02.

B. Upon written request, the board may grant a one-time waiver of the requirement of subsection A of this section for a period not to exceed one year due to demonstrated economic hardship, technological limitations that are not reasonably within the control of the prescriber, or other exceptional circumstances demonstrated by the prescriber.

Statutory Authority

§§54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 37, Issue 19, eff. June 9, 2021.

# Part II. Management of Acute Pain

## 18VAC85-21-30. Evaluation of the acute pain patient.

A. Nonpharmacologic and non-opioid treatment for pain shall be given consideration prior to treatment with opioids. If an opioid is considered necessary for the treatment of acute pain, the practitioner shall give a short-acting opioid in the lowest effective dose for the fewest possible days.

B. Prior to initiating treatment with a controlled substance containing an opioid for a complaint of acute pain, the prescriber shall perform a history and physical examination appropriate to the complaint, query the Prescription Monitoring Program as set forth in § 54.1-2522.1 of the Code of Virginia, and conduct an assessment of the patient's history and risk of substance misuse.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-40. Treatment of acute pain with opioids.

A. Initiation of opioid treatment for patients with acute pain shall be with short-acting opioids.

1. A prescriber providing treatment for acute painshall not prescribe a controlled substance containing an opioid in a quantity that exceeds a seven-day supply as determined by the manufacturer's directions for use,unless extenuating circumstances are clearly documented in the medical record. This shall also apply to prescriptions of a controlled substance containing an opioid upon discharge from an emergency department.

2. An opioid prescribed as part of treatment for a surgical procedure shall be for no more than 14 consecutive days in accordance with manufacturer's direction and within the immediate perioperative period, unless extenuating circumstances are clearly documented in the medical record.

B. Initiation of opioid treatment for all patients shall include the following:

1. The practitioner shall carefully consider and document in the medical recordthe reasons to exceed 50 MME/day.

2. Prior to exceeding 120 MME/day, the practitioner shall document in the medicalrecord the reasonable justification for such doses or refer to or consult with a pain management specialist.

3. Naloxone shall be prescribed for any patient when risk factors of prior overdose, substance misuse, doses in excess of 120 MME/day, or concomitant benzodiazepine are present.

C. Due to a higher risk of fatal overdose when opioids are prescribed with benzodiazepines, sedative hypnotics, carisoprodol, and tramadol (an atypical opioid), the prescriber shall only co-prescribe these substances when there are extenuating circumstances and shall document in the medical recorda tapering plan to achieve the lowest possible effective doses if these medications are prescribed.

D. Buprenorphine is not indicated for acute pain in the outpatient setting, except when a prescriber who has obtained a SAMHSA waiver is treating pain in a patient whose primary diagnosis is the disease of addiction.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-50. Medical records for acute pain.

The medical record shall include a description of the pain, a presumptive diagnosis for the origin of the pain, an examination appropriate to the complaint, a treatment plan, and the medication prescribed or administered to include the date, type, dosage, and quantity prescribed or administered.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## Part III. Management of Chronic Pain

### 18VAC85-21-60. Evaluation of the chronic pain patient.

A. Prior to initiating management of chronic pain with a controlled substance containing an opioid, a medical history and physical examination, to include a mental status examination, shall be performed and documented in the medical record, including:

1. The nature and intensity of the pain;

2. Current and past treatments for pain;

3. Underlying or coexisting diseases or conditions;

4. The effect of the pain on physical and psychological function, quality of life, and activities of daily living;

5. Psychiatric, addiction, and substance misuse history of the patient and any family history of addiction or substance misuse;

6. A urine drug screen or serum medication level;

7. A query of the Prescription Monitoring Program as set forth in § 54.1-2522.1 of the Code of Virginia;

8. An assessment of the patient's history and risk of substance misuse; and

9. A request for prior applicable records.

B. Prior to initiating opioid treatment for chronic pain, the practitioner shall discuss with the patient the known risks and benefits of opioid therapy and the responsibilities of the patient during treatment to include securely storing the drug and properly disposing of any unwanted or unused drugs. The practitioner shall also discuss with the patient an exit strategy for the discontinuation of opioids in the event they are not effective.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

### 18VAC85-21-70. Treatment of chronic pain with opioids.

A. Nonpharmacologic and non-opioid treatment for pain shall be given consideration prior to

treatment with opioids.

B. In initiating and treating with an opioid, the practitioner shall:

1. Carefully consider and document in the medical recordthe reasons to exceed 50 MME per day;

2. Prior to exceeding 120 MME per day, the practitioner shall document in the medical record the reasonable justification for such doses or refer to or consult with a pain management specialist;

3. Prescribe naloxone for any patient when risk factors of prior overdose, substance misuse, doses in excess of 120 MME per day, or concomitant benzodiazepine are present; and

4. Document the rationale to continue opioid therapy every three months.

C. Buprenorphine mono-product in tablet form shall not be prescribed for chronic pain.

D. Due to a higher risk of fatal overdose when opioids, including buprenorphine, are given with other opioids, benzodiazepines, sedative hypnotics, carisoprodol, and tramadol (an atypical opioid), the prescriber shall only co-prescribe these substances when there are extenuating circumstances and shall document in the medical record a tapering plan to achieve the lowest possible effective doses of these medications if prescribed.

E. The practitioner (i) shall regularly evaluate the patient for opioid use disorder and (ii) shall initiate specific treatment for opioid use disorder, consult with an appropriate health care provider, or refer the patient for evaluation and treatment if indicated.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-80. Treatment plan for chronic pain.

A. The medical record shall include a treatment plan that states measures to be used to determine progress in treatment, including pain relief and improved physical and psychosocial function, quality of life, and daily activities.

B. The treatment plan shall include further diagnostic evaluations and other treatment modalities or rehabilitation that may be necessary depending on the etiology of the pain and the extent to which the pain is associated with physical and psychosocial impairment.

C. The prescriber shall document in the medicalrecord the presence or absence of any indicators for medication misuse or diversion and shall take appropriate action.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-90. Informed consent and agreement for treatment for chronic pain.

A. The practitioner shall document in the medical record informed consent, to include risks, benefits, and alternative approaches, prior to the initiation of opioids for chronic pain.

B. There shall be a written treatment agreement signed by the patient in the medical record that addresses the parameters of treatment, including those behaviors that will result in referral to a higher level of care, cessation of treatment, or dismissal from care.

C. The treatment agreement shall include notice that the practitioner will query and receive reports from the Prescription Monitoring Program and permission for the practitioner to:

1. Obtain urine drug screens or serum medication levels when requested; and

2. Consult with other prescribers or dispensing pharmacists for the patient.

D. Expected outcomes shall be documented in the medical record including improvement in pain relief and function or simply in pain relief. Limitations and side effects of chronic opioid therapy shall be documented in the medical record.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-100. Opioid therapy for chronic pain.

A. The practitioner shall review the course of pain treatment and any new information about the etiology of the pain and the patient's state of health at least every three months.

B. Continuation of treatment with opioids shall be supported by documentation of continued benefit from such prescribing. If the patient's progress is unsatisfactory, the practitioner shall assess the appropriateness of continued use of the current treatment plan and consider the use of other therapeutic modalities.

C. The practitioner shall check the Prescription Monitoring Program at least every three months after the initiation of treatment.

D. The practitioner shall order and review a urine drug screen or serum medication levels at the initiation of chronic pain management and thereafter randomly at the discretion of the practitioner but at least once a year.

E. The practitioner (i) shall regularly evaluate the patient for opioid use disorder and (ii) shall initiate specific treatment for opioid use disorder, consult with an appropriate health care

provider, or refer the patient for evaluation for treatment if indicated.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-110. Additional consultations.

A. When necessary to achieve treatment goals, the prescriber shall refer the patient for additional evaluation and treatment.

B. When a prescriber makes the diagnosis of opioid use disorder, treatment for opioid use disorder shall be initiated or the patient shall be referred for evaluation and treatment.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-120. Medical records for chronic pain.

The prescriber shall keep current, accurate, and complete records in an accessible manner readily available for review to include:

1. The medical history and physical examination;

2. Past medical history;

3. Applicable records from prior treatment providers or any documentation of attempts to obtain those records;

4. Diagnostic, therapeutic, and laboratory results;

5. Evaluations and consultations;

6. Treatment goals;

7. Discussion of risks and benefits;

8. Informed consent and agreement for treatment;

9. Treatments;

10. Medications (including date, type, dosage, and quantity prescribed and refills);

11. Patient instructions; and

12. Periodic reviews.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## Part IV. Prescribing of Buprenorphine for Addiction Treatment

### 18VAC85-21-130. General provisions pertaining to prescribing of buprenorphine for addiction treatment.

A. Practitioners engaged in office-based opioid addiction treatment with buprenorphine shall have obtained a SAMHSA waiver and the appropriate U.S. Drug Enforcement Administration registration.

B. Practitioners shall abide by all federal and state laws and regulations governing the prescribing of buprenorphine for the treatment of opioid use disorder.

C. Physician assistants and nurse practitioners who have obtained a SAMHSA waiver shall only prescribe buprenorphine for opioid addiction pursuant to a practice agreement with a waivered doctor of medicine or doctor of osteopathic medicine.

D. Practitioners engaged in medication-assisted treatment shall either provide counseling in their practice or refer the patient to a mental health service provider, as defined in § 54.1-2400.1 of the Code of Virginia, who has the education and experience to provide substance misuse counseling. The practitioner shall document provision of counseling or referral in the medical record.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

### 18VAC85-21-140. Patient assessment and treatment planning for addiction treatment.

A. A practitioner shall perform and document an assessment that includes a comprehensive medical and psychiatric history, substance misuse history, family history and psychosocial supports, appropriate physical examination, urine drug screen, pregnancy test for women of childbearing age and ability, a check of the Prescription Monitoring Program, and, when clinically indicated, infectious disease testing for human immunodeficiency virus, hepatitis B, hepatitis C, and tuberculosis.

B. The treatment plan shall include the practitioner's rationale for selecting medication-assisted treatment, patient education, written informed consent, how counseling will be accomplished, and a signed treatment agreement that outlines the responsibilities of the patient and the

prescriber.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-150. Treatment with buprenorphine for addiction.

A. Buprenorphine without naloxone (buprenorphine mono-product) shall not be prescribed except:

1. When a patient is pregnant;

2. When converting a patient from methadone or buprenorphine mono-product to buprenorphine containing naloxone for a period not to exceed seven days;

3. In formulations other than tablet form for indications approved by the FDA; or

4. For patients who have a demonstrated intolerance to naloxone; such prescriptions for the mono-product shall not exceed 3.0% of the total prescriptions for buprenorphine written by the prescriber, and the exception shall be clearly documented in the patient's medical record.

B. Buprenorphine mono-product tablets may be administered directly to patients in federally licensed opioid treatment programs. With the exception of those conditions listed in subsection A of this section, only the buprenorphine product containingnaloxone shall be prescribed or dispensed for use off site from the program.

C. The evidence for the decision to use buprenorphine mono-product shall be fully documented in the medical record.

D. Due to a higher risk of fatal overdose when buprenorphine is prescribed with other opioids, benzodiazepines, sedative hypnotics, carisoprodol, and tramadol (an atypical opioid), the prescriber shall only co-prescribe these substances when there are extenuating circumstances and shall document in the medical record a tapering plan to achieve the lowest possible effective dosesif these medications are prescribed.

E. Prior to starting medication-assisted treatment, the practitioner shall perform a check of the Prescription Monitoring Program.

F. During the induction phase, except for medically indicated circumstances as documented in the medical record, patients should be started on no more than eight milligrams of buprenorphine per day. The patient shall be seen by the prescriber at least once a week.

G. During the stabilization phase, the prescriber shall increase the daily dosage of buprenorphine in safe and effective increments to achieve the lowest dose that avoids intoxication, withdrawal, or significant drug craving.

H. Practitioners shall take steps to reduce the chances of buprenorphine diversion by using the

lowest effective dose, appropriate frequency of office visits, pill counts, and checks of the Prescription Monitoring Program. The practitioner shall also require urine drug screens or serum medication levels at least every three months for the first year of treatment and at least every six months thereafter.

I. Documentation of the rationale for prescribed doses exceeding 16 milligrams of buprenorphine per day shall be placed in the medical record. Dosages exceeding 24 milligrams of buprenorphine per day shall not be prescribed.

J. The practitioner shall incorporate relapse prevention strategies into counseling or assure that they are addressed by a mental health service provider, as defined in § 54.1-2400.1 of the Code of Virginia, who has the education and experience to provide substance misuse counseling.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-160. Special populations in addiction treatment.

A. Pregnant women may be treated with the buprenorphine mono-product, usually 16 milligrams per day or less.

B. Patients younger than the age of 16 years shall not be prescribed buprenorphine for addiction treatment unless such treatment is approved by the FDA.

C. The progress of patients with chronic pain shall be assessed by reduction of pain and functional objectives that can be identified, quantified, and independently verified.

D. Practitioners shall (i) evaluate patients with medical comorbidities by history, physical exam, and appropriate laboratory studies and (ii) be aware of interactions of buprenorphine with other prescribed medications.

E. Practitioners shall not undertake buprenorphine treatment with a patient who has psychiatric comorbidities and is not stable. A patient who is determined by the prescriber to be psychiatrically unstable shall be referred for psychiatric evaluation and treatment prior to initiating medication-assisted treatment.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

## 18VAC85-21-170. Medical records for opioid addiction treatment.

A. Records shall be timely, accurate, legible, complete, and readily accessible for review.

B. The treatment agreement and informed consent shall be maintained in the medical record.

C. Confidentiality requirements of 42 CFR Part 2 shall be followed.

D. Compliance with 18VAC85-20-27, which prohibits willful or negligent breach of confidentiality or unauthorized disclosure of confidential Prescription Monitoring Program information, shall be maintained.

Statutory Authority

§§ 54.1-2400 and 54.1-2928.2 of the Code of Virginia.

Historical Notes

Derived from Virginia Register Volume 34, Issue 23, eff. August 8, 2018.

Morbidity and Mortality Weekly Report (*MMWR*)

Morbidity and Mortality Weekly Report (MMWR) Home

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

*Recommendations and Reports* / November 4, 2022 / 71(3);1–95

## 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.*

Related Materials

Prescribing Opioids for Pain — The New CDC Clinical Practice Guideline

MMWR Article PDF [1 MB]

Deborah Dowell, MD[1]; Kathleen R. Ragan, MSPH[1]; Christopher M. Jones, PharmD, DrPH[2]; Grant T. Baldwin, PhD[1]; Roger Chou, MD[3] (VIEW AUTHOR AFFILIATIONS)Top

View suggested citation

# 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.

## Scope and Audience

This clinical practice guideline is intended for clinicians who are treating outpatients aged ≥18 years with acute (duration of <1 month), subacute (duration of 1–3 months), or chronic (duration of >3 months) pain, and excludes pain management related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care. The recommendations are most relevant to clinicians whose scope of practice includes prescribing opioids (e.g., physicians, nurse practitioners and other advanced-practice registered nurses, physician assistants, and oral health practitioners). Because clinicians might work within team-based care, this clinical practice guideline also refers to and promotes integrated pain management and collaborative working relationships among clinicians (e.g., behavioral health specialists such as social workers or psychologists, pharmacists, and registered nurses). This guideline update includes recommendations for primary care clinicians (e.g., internists and family physicians) and other clinicians managing pain in outpatient settings (e.g., surgeons, emergency medicine clinicians, occupational medicine clinicians, physical medicine and rehabilitation clinicians, and neurologists). Applicable settings include clinician offices, clinics, and urgent care centers. The recommendations do not apply to care provided to patients who are hospitalized or in an emergency department or other observational setting from which they might be admitted to inpatient care. These recommendations do apply to prescribing for pain management for patients when they are discharged from hospitals, emergency departments, or other facilities.

In addition to updating recommendations on the basis of new evidence regarding management of chronic pain, this clinical practice guideline is intended 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, kidney stone pain, and acute episodic migraine) and pain related to procedures (e.g., postoperative pain and pain from oral surgery). In 2020, several of these indications were prioritized by an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (*86*) as those for which evidence-based clinical practice guidelines would help inform prescribing practices, with the greatest potential effect on public health. This update includes content on management of subacute painful conditions, when duration falls between that typically considered acute (defined as lasting <1 month) and chronic (defined as lasting >3 months). 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. These time-bound definitions are not meant to be absolute but rather to be approximate guides to facilitate the consideration and practical use of the recommendations by clinicians and patients.

The 2016 CDC Opioid Prescribing Guideline focused on recommendations for primary care physicians. This clinical practice guideline expands the scope to additional clinicians. Although primary care physicians prescribe approximately 37% of all opioid prescriptions, other clinicians, including pain medicine clinicians (8.9%) and dentists (8.6%), account for considerable proportions of prescriptions. Pain medicine and physical medicine and rehabilitation clinicians prescribe opioids at the highest rates, followed by orthopedic and family medicine clinicians (*83*). Thus, expanding the 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. 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 treat patients with clinical situations that are more complex, less prevalent, and not well addressed by the available evidence; therefore, the balance of benefits and risks to patients might differ when the treating clinician is a pain management specialist.

The recommendations address the use of opioid pain medication in certain special populations (e.g., older adults and pregnant persons) and in populations with conditions posing special risks (e.g., a history of a 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 their labeling regarding safety and effectiveness in pediatric patients. Guidelines and recommendations are available for pain management in children with sickle cell disease (*87*), for children undergoing surgical procedures (*88*), and for palliative care in adolescent and young adult patients with cancer (*89*).

Although some principles in this clinical practice guideline might be helpful in the management of pain related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care, some recommendations might not be relevant for pain management in these contexts. Other guidelines more specifically address pain management in these situations (*87,89–93*); therefore, this clinical practice guideline does not apply to patients experiencing pain associated with these conditions or types of care. This does not imply that any other types of pain are more or less worthy of effective treatment, only that clinicians are referred to existing clinical guidelines that more specifically address unique considerations for management of pain related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care.

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 (*94*). Palliative care can begin early in the course of treatment for any serious illness that requires advanced management of pain or other distressing symptoms (*94*). In this guideline, end-of-life care refers to care for persons in hospice care and others with a terminal illness or at high risk for dying in the near future in hospitals, receiving long-term services and supports (including institutional care and home- and community-based services), or at home. This clinical practice guideline does not apply to patients undergoing cancer-related pain treatment, palliative care, or end-of-life care because of the unique therapeutic goals, ethical considerations, opportunities for medical supervision, and balance of benefits and risks with opioid therapy in such care. For example, for many persons at the end of life, serious potential long-term opioid-related harms such as opioid use disorder might not be relevant.

Recommendations on pain management for patients with cancer and patients who have survived cancer are available in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Adult Cancer Pain (*90*), NCCN Clinical Practice Guidelines in Oncology: Survivorship (*91*), and Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology (ASCO) Clinical Practice Guideline (*92*). Because of unique considerations in management of pain related to sickle cell disease, which can change the balance of benefits and risks of the use of opioids, clinicians should refer to the American Society of Hematology (ASH) 2020 Guidelines for Sickle Cell Disease: Management of Acute and Chronic Pain (*87*). In 2018, NCCN and ASCO convened and led a meeting including representatives and guideline authors from NCNN, ASCO, ASH, and CDC to review existing pain management guidelines and guidelines then in development from these organizations (*56,87,90–92*). Meeting participants noted that these guidelines applied to different patient populations and target audiences but found no disagreement among recommendations when applied to the appropriate patient and clinical situation (*95*).

Although this update includes content on pain management for patients with opioid use disorder and one recommendation 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. More detailed recommendations on management of patients with opioid use disorder are available in the American Society of Addiction Medicine (ASAM) National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update (*96*).

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# Clinical Practice Guideline Development Methods

## Systematic Reviews and Evidence Sources

The 2016 CDC Opioid Prescribing 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 (*47,97*), a CDC update to the AHRQ-sponsored review, and additional contextual questions (*56,98*). The 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 prescription opioid misuse. The CDC update to the AHRQ-sponsored review included 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 about resource allocation.

For this update to the 2016 CDC Opioid Prescribing Guideline, CDC funded AHRQ in 2018 and 2019 to conduct five systematic reviews (*7–11*). AHRQ's Evidence-based Practice Centers completed these reviews, which included new evidence related to the treatment of chronic and acute pain. The AHRQ review of opioids for chronic pain updated and expanded the evidence for the 2016 CDC review; studies were included on short-term (1 to <6 months), intermediate-term (6 to <12 months) and long-term (≥12 months) outcomes of therapy involving opioids, effects of opioid plus nonopioid combination therapy, effects of tramadol, effects of naloxone coprescription, risks of coprescribed benzodiazepines, risks of coprescribed gabapentinoids, and effects of concurrent use of cannabis (*7*). The systematic clinical evidence review on opioids for chronic pain (*7*) also included contextual questions on clinician and patient values and preferences, costs and cost-effectiveness of opioid therapy, and risk mitigation strategies. CDC considered four new complementary AHRQ reviews on the benefits and harms of nonpharmacologic treatments for chronic pain (*9*), nonopioid pharmacologic treatments for chronic pain (*8*), treatments for acute episodic migraine (*11*), and treatments for acute (nonmigraine) pain (*10*). A question on management of acute pain in the systematic clinical evidence review for the 2016 CDC Opioid Prescribing Guideline was included in the new review on therapies for acute pain (*10*). 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. 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 (*8–11*).

## AHRQ Method for Evaluating Quality of Evidence

The reviews used the AHRQ approach to synthesize and grade the strength of evidence (*99*). 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); similar factors are considered in the Advisory Committee on Immunization Practices (ACIP) adapted (*100,101*) Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (*102*) method. These factors include study limitations and risk for bias, consistency, directness, precision, and reporting bias. Large strength of association, dose response, and plausible confounders can strengthen observed findings. The primary clinical questions, detailed methods, and findings for the systematic and contextual evidence reviews are presented (Appendix).

## ACIP Adapted GRADE Method for Evaluating Quality of Evidence

The GRADE method is predicated on a systematic review of scientific evidence and provides a transparent framework for grading the quality of evidence and strength of recommendations. GRADE has been adapted by ACIP (*100,101*), and CDC used the ACIP adaptation in this clinical practice guideline. Under 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 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) (Box 3). The evidence is downgraded if issues are identified with regard to risk for bias, inconsistency, indirectness, imprecision, or publication bias. Observational studies might be upgraded in certain situations (large strength of association, presence of dose response, or plausible effects of confounding would strengthen findings; that is, if confounding would likely provide results opposite to the observed findings, it strengthens the confidence that the observed association is present). A final evidence type is assigned based on these considerations. 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 very little confidence in the effect estimate (high uncertainty), and the likelihood is high that the true effect differs from the estimate of the effect (*100,103*). When no studies are available or the evidence is too limited to estimate effects, evidence is considered insufficient.

## Categorizing the Evidence

The AHRQ approach uses a different method and terminology (high, moderate, low, or insufficient) to grade the strength of evidence from the ACIP adapted GRADE method (evidence types 1, 2, 3, or 4) (*99*). However, the underlying principles are similar, enabling translation from AHRQ to CDC grades. A methodologist translated the AHRQ strength of evidence grades to CDC evidence types according to 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 (https://stacks.cdc.gov/view/cdc/121663). Evidence was categorized into the following types: type 1 (randomized clinical trials or overwhelming evidence from observational studies; equivalent to AHRQ high strength of evidence), type 2 (randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies; equivalent to AHRQ moderate strength of evidence), type 3 (observational studies, or randomized clinical trials with notable limitations; 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.

## Recommendation Development

CDC developed this clinical practice guideline using the method 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: 1) the quality of evidence, 2) the balance between desirable and undesirable effects, 3) values and preferences, and 4) resource allocation (e.g., costs to patients or health systems) (*104*). Other considerations include feasibility and acceptability and effect on equity (*105*). Recommendations are more likely to be category A when the evidence is higher quality, a balance of desirable relative to undesirable effects is greater, resources and costs are lower, and recommendations are less sensitive to differences in values and preferences. Category A recommendations typically 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 might 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 made based on the 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) (*106*). In the GRADE method, a particular quality of evidence does not necessarily result in a particular strength of recommendation (*102–104*). Although it is desirable for category A recommendations to be based on type 1 or type 2 evidence, category A recommendations can be based on type 3 or type 4 evidence when the advantages of a clinical action clearly outweigh the disadvantages in terms of benefits and harms, values and preferences, and costs, despite uncertainty in effect estimates (*104*). The GRADE working group has presented several paradigmatic situations in which strong (category A) recommendations might be justified despite low-quality evidence (e.g., 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- or very low–quality evidence suggests possibility of catastrophic harm) (*104*). Category B recommendations are made when the advantages and disadvantages of a clinical action are more balanced or when more uncertainty exists with regard to whether benefits clearly outweigh harms.

In accordance with the ACIP adapted GRADE method, CDC drafted evidence-based recommendations focused on determining whether or not to initiate opioids for pain, selecting opioids and determining opioid dosages, deciding duration of initial opioid prescription and conducting 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.

## Federal Advisory Committee Review and Recommendation

CDC sought recommendations on the draft 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). BSC/NCIPC advises the U.S. Department of Health and Human Services (HHS) Secretary, the CDC Director, and the NCIPC Director and makes recommendations regarding scientific, programmatic, and research policies, strategies, objectives, projects, and priorities. BSC/NCIPC also reviews progress toward injury and violence prevention. BSC/NCIPC members are special government employees appointed by the HHS Secretary 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 BSC/NCIPC are reported in this clinical practice guideline. Meeting minutes and documents for public BSC/NCIPC meetings are available on the BSC/NCIPC website (https://www.cdc.gov/injury/bsc/meetings.html).

On December 4–5, 2019, CDC held a public meeting of 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 clinical practice guideline and to develop a report of their observations for BSC/NCIPC (*107*). After considering CDC's presentations, the proposed OWG Terms of Reference, and public comments, BSC/NCIPC voted unanimously to establish an OWG that reports to BSC/NCIPC. CDC then held a public nomination process for prospective OWG members (*107*).

To provide background to BSC/NCIPC for informing the creation of 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 BSC/NCIPC. Identified groups with perspectives that would support the workgroup's capacity included, but were not limited to, patients 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. Persons 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 OWG.

After reviewing clinical expertise, professional credentials, and diversity in perspectives of all nominees (including diversity of gender, race and ethnicity, geographic region, institutional affiliations, and personal experiences relevant to pain management and providing care to patients with pain), OWG's Designated Federal Officer (DFO) created a list of prospective workgroup members and sent them invitations to participate, along with conflict of interest disclosure forms. OWG's DFO and 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 nonsignificant before finalizing selection.* OWG members disclosed any potential topical conflicts of interest related to OWG meeting agenda items before each meeting. Disclosures of OWG are reported in the clinical practice guideline.

OWG had 23 members (*108*) including four ex officio members representing federal partner agencies (see Federal Partner Engagement). In accordance with CDC guidance (*109,110*) that at least two BSC/NCIPC members must serve on OWG and one of the two members must serve as the workgroup chair, OWG included a total of three BSC/NCIPC members, with one BSC/NCIPC member serving as the OWG chair. An NCIPC subject matter expert served as OWG's DFO. OWG members included patients with pain, caregivers, and family members of patients with pain. 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 gender, race and 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).

OWG had 11 meetings from October 2020 through June 2021. Before receiving the draft clinical practice guideline, OWG held meetings to review and discuss the 2016 CDC Opioid Prescribing Guideline; CDC's community engagement activities with patients, caregivers, and clinicians; and GRADE methodology. CDC NCIPC staff provided OWG with evidence reviews, public comments from BSC/NCIPC meetings, and summaries of community engagements for review before providing OWG with the draft clinical practice guideline in March 2021. OWG held seven meetings to review and discuss the draft clinical practice guideline and develop a report summarizing their expert observations and findings for BSC/NCIPC. The OWG report provided overall observations on overarching themes and draft clinical practice guideline recommendations (*111*). In addition, many members of 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 OWG approached their assigned tasks." These *Guiding Principles* included minimizing bias, ensuring scientific integrity, enhancing inclusivity, being patient and clinician centered, and considering historical context.

The OWG chair presented the OWG report at a public BSC/NCIPC meeting 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 2-hour public comment period, BSC/NCIPC voted unanimously that CDC adopt the OWG report, while considering ideas and suggestions raised by BSC/NCIPC and the public during the meeting, and that OWG's work be considered complete and that OWG be sunsetted. BSC/NCIPC provided their recommendations to HHS and CDC on July 20, 2021. CDC considered OWG's observations, BSC/NCIPC recommendations, and public comments during BSC/NCIPC meetings when revising the draft clinical practice guideline (*112,113*). A list of BSC/NCIPC and of OWG members appears at the end of this report. The recommendations and all statements included in this guideline are those of CDC and do not necessarily represent the official position of any persons or organizations providing comments on this guideline.

## Federal Partner Engagement

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

## Public Comment and Community Engagement

CDC sought input through *Federal Register* notices to better understand community members' experiences and perspectives related to pain and pain management options before drafting the clinical practice guideline (*113*). Through the *Federal Register* notice (85 FR 21441) posted from April 17, 2020, through June 16, 2020, CDC invited input specifically on topics focused on using or prescribing opioid pain medications, nonopioid medications, or nonpharmacologic treatments and received 5,392 public comments. Public comments were synthesized into common themes, using a CDC-funded analysis contract, and reviewed by CDC.

In addition, the Lab at the U.S. Office of Personnel Management (OPM) (https://lab.opm.gov) worked with CDC to design and implement community engagement opportunities. These opportunities were designed to gain additional insight into the values and preferences of groups including patients with acute or chronic pain, patients' family members 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 in-person individual conversations with patients, caregivers, and clinicians but pivoted to holding conversations with persons in a virtual format because of 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, and clinicians) from 973 respondents. CDC and OPM also developed a randomly selected waiting list of participants to fill conversation appointments that were missed or canceled 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 persons, including 42 patients, 21 caregivers, and 43 clinicians. Participants 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 codesign workshops with staff from CDC and the Centers for Medicare & Medicaid Services. Workshop topics included framing priority needs for public input; objectives for individual conversations; and synthesizing engagement strategies on the basis of insights from public comments and conversations with patients, caregivers, and clinicians. Workshop participants included HHS staff who were themselves patients, caregivers, clinicians, clinical practice guideline authors, and other subject matter experts.

CDC also gathered 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 NCIPC newsletters.

CDC reviewed thematic summaries of public comments, individual conversations, and workshops to learn more about values and preferences of patients, caregivers, clinicians, and experts before drafting the clinical practice guideline (*113*). After incorporating observations and comments on the draft clinical practice guideline from BSC/NCIPC and the agency clearance process, CDC posted the revised full draft clinical practice guideline and supporting materials in the *Federal Register* for public comment (*Federal Register* 87 FR 7838). The public comment period was open for 60 days (February 10–April 11, 2022). The Federal Docket received approximately 5,500

unique comments (including one comment submitted with 28,322 additional signatories) from the public, including patients with acute and chronic pain, caregivers, and clinicians, and organizational perspectives from medical associations, professional organizations, academic institutions, state and local governments, and advocacy and industry groups. CDC reviewed and considered all public comments when revising the clinical practice guideline.

## Peer Review

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

CDC identified peer reviewers on the basis of multiple factors, including scientific and subject matter expertise, racial and ethnic diversity, gender 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, pharmacologic and nonpharmacologic pain management, and surgical pain management. CDC assessed potential conflicts of interest before finalizing selection of peer reviewers. The NCIPC Associate Director for Science reviewed conflict of interest disclosure forms and determined no conflicts of interest were present. After the peer reviews were completed, CDC posted the names of peer reviewers on the NCIPC and CDC/ATSDR Peer Review Agenda websites, which provide information about the peer review of influential government scientific documents (*114,115*). Peer reviewers independently reviewed the draft clinical practice guideline and evaluated its scientific merit and practical implementation considerations, with the goal of maintaining high-quality science and providing evidence-based recommendations to guide clinical practice and decision-making to help prevent opioid-related harms. CDC reviewed and considered peer review comments when revising the clinical practice guideline.

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# Recommendations

This clinical practice guideline includes 12 recommendations for clinicians who are prescribing opioids for outpatients aged ≥18 years with acute (duration of <1 month), subacute (duration of 1–3 months), or chronic (duration of >3 months) pain, excluding pain management related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care (Box 3). The recommendations are not intended to be implemented as absolute limits of policy or practice across populations by organizations, health care systems, or government entities. In accordance with the ACIP adapted GRADE method, CDC based the recommendations on consideration of clinical evidence, contextual evidence (e.g., benefits and harms, values and preferences, and 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 evidence (1, 2, 3, or 4) supporting the statement (Box 3).

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 (*106,116*) and GRADE method (*103*), 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. 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 nonpharmacologic treatments and nonopioid medications are associated with improvements in pain, function, or both that are reportedly comparable to improvements associated with opioid use (*7–11*).
- Evidence exists that multiple 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 after patients stop taking the medication, multiple noninvasive nonpharmacologic interventions are associated with improvements in pain, function, or both that are sustained after completion of treatment (*9*).
- Nonopioid drugs, including serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants, pregabalin or gabapentin, and nonsteroidal anti-inflammatory drugs (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 (*8*).
- Opioid therapy is associated with similar or decreased effectiveness for pain and function versus NSAIDs across multiple common acute pain conditions (*10*). Opioid therapy is associated with small improvements in short-term (duration of 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) (*10*). Evidence exists from observational studies of an association between opioid use for acute pain and long-term opioid use (*10*). Evidence on long-term effectiveness of opioids remains very limited (*7*); 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 with starting with nonopioid therapy (*74*). Evidence exists of increased risk for serious harms (including opioid use disorder and overdose) with long-term opioid therapy that appears to rise with increase in opioid dosage, without a clear threshold below which there is no risk (*7*).
- No validated, reliable way exists to predict which patients will experience serious harm from opioid therapy and which patients will benefit from opioid therapy (*7*).
- Discontinuing opioids after extended periods of continuous opioid use can be challenging for clinicians and patients. Tapering or discontinuing opioids in patients who have taken them long term can be associated with clinically significant risks (*68*), particularly if opioids are tapered rapidly or patients do not receive effective support.
- Patients, caregivers, and clinicians responded to CDC with invited input about their experiences and perspectives related to pain and pain management options. Themes included strained patient-clinician relationships and the need for patients and clinicians to make shared decisions, the effects of misapplication of the 2016 CDC Opioid Prescribing Guideline, inconsistent access to effective pain management solutions, and achieving reduced prescription opioid use through diverse approaches.
- Members of the public responded to CDC with invited comments. Themes included experiences with pain or experiences in the aftermath of the overdose of a friend, family member, or significant other; barriers and access to pain care and to evidence-based treatment; concerns about the level of specificity of recommendations; and overall communication and implementation of the clinical practice guideline.

Each of the 12 recommendation statements is followed by considerations for implementation and a rationale for the recommendation. The implementation considerations offer practical insights, context, and specific examples 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:

1. Determining whether or not to initiate opioids for pain
2. Selecting opioids and determining dosages
3. Deciding duration of initial opioid prescription and conducting follow-up
4. Assessing risk and addressing potential harms of opioid use

In addition, these five guiding principles should broadly inform implementation across recommendations (Box 4):

1. Acute, subacute, and chronic pain needs to be appropriately assessed and 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 is 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 clinical practice guideline beyond its intended use or implementing policies purportedly derived from it that might lead to unintended and potentially harmful consequences for patients.
5. Clinicians, practices, health systems, and payers should vigilantly attend to health inequities; provide culturally and linguistically appropriate communication (*117*), 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 or not to initiate opioids for acute pain [i.e., pain lasting <1 month] and Recommendation 2 for determining whether or not to initiate opioids for subacute pain [i.e., pain lasting 1–3 months] or chronic pain [i.e., pain lasting >3 months].)

### Recommendation 1

**Nonopioid therapies are at least as effective as opioids for many common types of acute pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient. Before prescribing opioid therapy for acute pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy (recommendation category: B; evidence type: 3).**

#### Implementation Considerations

- Nonopioid therapies are at least as effective as opioids for many common acute pain conditions, including low back pain, neck pain, pain related to other musculoskeletal injuries (e.g., sprains, strains, tendonitis, and bursitis), pain related to minor surgeries typically associated with minimal tissue injury and mild postoperative pain (e.g., simple dental extraction), dental pain, kidney stone pain, and headaches including episodic migraine.
- Clinicians should maximize use of nonopioid pharmacologic (e.g., topical or oral NSAIDs, acetaminophen) and nonpharmacologic (e.g., ice, heat, elevation, rest, immobilization, or exercise) therapies as appropriate for the specific condition.
- Opioid therapy has an important role 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 warrant the use of opioids, clinicians should prescribe immediate-release opioids (see Recommendation 3) at the lowest effective dose (see Recommendation 4) and for no longer than the expected duration of pain severe enough to require opioids (see Recommendation 6).
- Clinicians should prescribe and advise opioid use only as needed (e.g., hydrocodone 5 mg/acetaminophen 325 mg, one tablet not more frequently than every 4 hours as needed for moderate to severe pain) rather than on a scheduled basis (e.g., one tablet every 4 hours) and encourage and recommend an opioid taper if opioids are taken around the clock for more than a few days (see Recommendation 6).
- If patients already receiving opioids long term 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 risks of, 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 to 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 (e.g., surgical intervention to repair structure and function after 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) (*118*).

### Noninvasive Nonpharmacologic Approaches to Acute Pain

Noninvasive nonpharmacologic approaches to acute pain have the potential to improve pain and function without risk for serious harms (*10*). Clinical evidence reviews found that some nonpharmacologic treatments were likely effective for acute pain, such as heat therapy for acute low back pain; several others might be effective for specific acute pain conditions, such as spinal manipulation for acute back pain with radiculopathy, a cervical collar or exercise for acute neck pain with radiculopathy, acupressure for acute musculoskeletal pain, massage for postoperative pain (*10*), and remote electrical neuromodulation for acute pain related to episodic migraine (*11*).

The American College of Physicians (ACP) recommends nonpharmacologic treatment with superficial heat, massage, acupuncture, or spinal manipulation as a cornerstone of treatment for acute low back pain (*119*). ACP and the American Academy of Family Physicians (AAFP) suggest acupressure to improve pain and function and transcutaneous electrical nerve stimulation to reduce pain in patients with acute musculoskeletal injuries (*120*).

Despite evidence supporting their use, noninvasive nonpharmacologic therapies are not always or fully covered by insurance (*43*), and access and cost can be barriers, particularly for persons who are uninsured, have limited income, have transportation challenges, or live in rural areas where treatments are not available (*121*). Experts from OWG expressed concern about limited access to nonopioid pain management modalities, in part because of lack of availability or lack of coverage by payers, and emphasized improving access to nonopioid pain management modalities as a priority. Health insurers and health systems can contribute to improved pain

management and reduced medication use by increasing access to noninvasive nonpharmacologic therapies with evidence of effectiveness (*9,43*). 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 often can be managed most effectively with nonopioid medications (*10,122*). A systematic review found that for musculoskeletal injuries such as sprains, whiplash, and muscle strains, topical NSAIDs provided the greatest benefit-harm ratio, followed by oral NSAIDs or acetaminophen with or without diclofenac (*122*). NSAIDs have been found to be more effective than opioids for surgical dental pain and kidney stone pain and similarly effective to opioids for low back pain (*10*). Evidence is limited on comparative effectiveness of therapies for acute neuropathic pain, neck pain, and postoperative pain (*10*). For episodic migraine, triptans, NSAIDs, antiemetics, dihydroergotamine, calcitonin gene-related peptide antagonists (gepants), and lasmiditan are associated with improved pain and function with usually mild and transient adverse events (*11*).

ACP recommends NSAIDs or skeletal muscle relaxants if pharmacologic treatment is desired to treat low back pain (*119*). For acute musculoskeletal injuries other than low back pain, ACP and AAFP recommend topical NSAIDs with or without menthol gel as first-line therapy and suggest oral NSAIDs to relieve pain or improve function or oral acetaminophen to reduce pain (*120*). The American Dental Association (ADA) recommends NSAIDs as first-line treatment for acute dental pain management (*123*). For acute kidney stone pain, NSAIDs are at least as effective as opioids (*124–127*), can decrease the ureteral smooth muscle tone and ureteral spasm (*128*) causing kidney stone pain, and are preferred for kidney stone pain if not contraindicated. Triptans, NSAIDs, combined triptans with NSAIDs, antiemetics, dihydroergotamine, and acetaminophen are established acute treatments for migraine (*11*). Lasmiditan, an 5-HT1F receptor agonist, and ubrogepant, a gepant, were approved by FDA in 2019 for the treatment of migraine (*129*); 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 1 week (*11*). Adverse events related to these newer medications require further study; however, their mechanisms of action are believed to be nonvasoconstrictive (*130*) and potentially carry lower risks than vasoactive medications in patients with cardiovascular risk factors (*11*).

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 stone pain; 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 (*8*), particularly in patients with cardiovascular or gastrointestinal comorbidities, 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, 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 (*11,131,132*). Clinicians should review FDA-approved labeling, including boxed warnings, before initiating treatment with any pharmacologic therapy.

### Pain Management for Pregnant and Postpartum Persons

For pain management in the postpartum period, the American College of Obstetricians and Gynecologists (ACOG) recommends stepwise, multimodal, shared decision-making, incorporating pharmacologic treatments that might include opioids. After vaginal delivery, ACOG recommends acetaminophen or NSAIDs, and if needed, adding an opioid. After cesarean delivery, ACOG recommends standard oral and parenteral medications such as acetaminophen, NSAIDs, or low-dose, low-potency, short-acting opioids with duration of opioid use limited to the shortest reasonable course expected for treating acute pain (*133*). ACOG recommends counseling persons who are prescribed opioids about the risk for central nervous system depression in the postpartum person and in the breastfed infant (*133*), noting that if a codeine-containing medication is selected, duration of therapy and neonatal signs of toxicity should be reviewed with patients and their families (*133*).

### Opioid Medication for Acute Pain

A systematic review found that for musculoskeletal injuries such as sprains, whiplash, and muscle strains, no opioid provided better benefit than NSAIDs, and opioid use caused the most harms (*122*). The evidence review (*10*) found that opioids might not be more effective than nonopioid therapies for some acute pain conditions (*134–138*), and use of opioids might negatively affect recovery and function (*139,140*). The review found that opioids were probably less effective than NSAIDs for surgical dental pain and kidney stone pain, less effective than acetaminophen for kidney stone pain, and similarly effective as NSAIDs for low back pain (*10*). For postoperative pain, effects of opioids on pain intensity were inconsistent, and opioids were associated with increased likelihood of repeat or rescue analgesic use (*10*). Evidence was insufficient for opioids in treatment of episodic migraine (*11*). Compared with NSAIDs or acetaminophen, opioids were associated with increased risk for short-term adverse events, including any adverse event, nausea, dizziness, and somnolence (*10*). Observational studies found that opioid use for acute low back pain or postoperative pain was associated with increased likelihood of long-term opioid use (*10*). Proportions of adults with new long-term opioid use at follow-up after initiation for short-term use for postoperative pain have ranged from <1% to 13% (*141–146*). Odds of long-term opioid use at follow-up after initiation for short-term use for acute pain might be greater with higher dosage and longer initial 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: 1.55–2.78) for an early prescription totaling 1–140 MME and increased to 6.14 (95% CI: 4.92–7.66) for an early prescription totaling ≥450 MME (*140*). In episodic migraine, opioids as well as butalbital-containing medications were associated with a twofold higher risk for development of medication overuse headache compared with simple analgesics and triptans (*11,147*). Serious adverse events were uncommon for opioids and other medications; however, studies were not designed to assess risk for overdose, opioid use disorder, or long-term harms (*10*).

For acute low back pain, ACP found insufficient evidence for effectiveness of opioids and recommends nonopioid medications (see Nonopioid Medications for Acute Pain) if choosing pharmacologic treatment (*119*). ACP and AAFP suggest against treating patients with acute pain from musculoskeletal injuries with opioids, including tramadol (*120*). ADA recommends NSAIDs as the first-line therapy for acute pain management (see Nonopioid Medications for Acute Pain) (*123*). Multiple guidelines that address 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 often are needed postoperatively but are not required in all patients (*148–151*). The American Headache Society recommends against prescribing opioid or butalbital-containing medications as first-line treatment for recurrent headache disorders (*152*), and the American Academy of Neurology also recommends against use of both of these classes of medications for treatment of migraine, except as a last resort (*153*).

Because of equivalent or lesser effectiveness for pain relief compared with NSAIDs and risks for 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 (e.g., sprains, strains, tendonitis, and bursitis), pain related to minor surgeries typically associated with minimal tissue injury and only mild postoperative pain (e.g., simple dental extraction), dental pain, kidney stone pain, and headaches including episodic migraine. Opioid therapy† has an important role 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 warrant the use of opioids, clinicians should prescribe immediate-release opioids (see Recommendation 3) at the lowest effective dose (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, acetaminophen, or both) and nonpharmacologic (e.g., ice, heat, elevation, rest, immobilization, or exercise) therapies as appropriate for the specific condition and continue these therapies as needed after 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 325 mg, one tablet not more frequently than every 4 hours as needed for moderate to severe 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 disorders, in assessing risks of opioid therapy (see Recommendation 8); offer naloxone, particularly if the patient or a household member has risk factors for opioid overdose (see Recommendation 8); use particular caution when prescribing benzodiazepines or other sedating medications with opioid pain medication (see Recommendation 11); and check the prescription drug monitoring program (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 signs of opioid use disorder are present, clinicians should address concerns with the patient, offer or arrange medication treatment for patients who meet criteria for opioid use disorder, and 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) (*96*).

Although findings regarding risks for new long-term opioid use after use for acute pain (*10*) relate specifically to patients who were previously opioid naïve, risks also might be associated with dosage 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 receiving long-term opioid therapy require additional medication for acute pain, nonopioid medications should be used when possible. 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 used to inform clinical decisions. Clinicians should ensure that patients are aware of expected benefits of, common risks of, 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 prescribing 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 of 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 tell 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 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. Prophylactic pharmacologic therapy (e.g., a stimulant laxative such as senna, with or without a stool softener) might be needed to ensure regular bowel movements if opioids are used for more than a few days. Stool softeners or fiber laxatives without another laxative should be avoided. 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 withdrawal after 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.
- 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 a person's ability to safely operate a vehicle or other machinery, particularly when opioids are initiated or when other central nervous system depressants (e.g., benzodiazepines or alcohol) are used concurrently.
- Discuss the potential for workplace toxicology testing programs to detect therapeutic opioid use.
- 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 than prescribed or taking them more often).
- Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, nonprescribed or illicit drugs (e.g., heroin), or other opioids (see Recommendations 8 and 11).
- Discuss risks to household members and other persons 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 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 and preferably locked location, options for safe disposal of unused opioids (*154*), and the value of having naloxone available.
- Discuss planned use of precautions to reduce risks, including naloxone for overdose reversal (see Recommendation 8) and clinician use of PDMP information (see Recommendation 9).

### Recommendation 2

**Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and 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 realistic benefits and known risks 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 recommend appropriate noninvasive nonpharmacologic approaches to help manage chronic pain, such as exercise (e.g., aerobic, aquatic, 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 (e.g., yoga, tai chi, or qigong), massage, and acupuncture for neck pain; cognitive behavioral therapy, 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 whose pain has not improved with low-intensity physical exercise.

- Health insurers and health systems can improve pain management and reduce medication use and associated risks by increasing reimbursement for and 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 pain in a single or few joints near the surface of the skin (e.g., knee). For 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 effective dose and shortest duration needed and should be used with caution, particularly in older adults and 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 (e.g., pregabalin, gabapentin enacarbil, oxcarbazepine); and capsaicin and lidocaine patches can be considered for neuropathic pain. In older adults, decisions to use tricyclic antidepressants should be made judiciously on a case-by-case basis because of risks for confusion and falls.
- Duloxetine and pregabalin are FDA-approved for the treatment of diabetic peripheral neuropathy, and pregabalin and gabapentin are FDA-approved for treatment of postherpetic neuralgia.
- In patients with fibromyalgia, tricyclic (e.g., amitriptyline) and SNRI antidepressants (e.g., duloxetine, milnacipran), NSAIDs (e.g., topical diclofenac), and specific anticonvulsants (i.e., 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. In older adults, decisions to use tricyclic antidepressants should be made judiciously on a case-by-case basis because of risks for confusion and falls.
- 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 treatment 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 functional benefit will be evaluated and establish specific, measurable treatment goals.
- For patients with subacute pain who started opioid therapy for acute pain and have been treated with opioid therapy for ≥30 days, clinicians should ensure that potentially reversible causes of chronic pain are addressed and that opioid prescribing for acute pain does not unintentionally become long-term opioid therapy simply because medications are continued without reassessment. Continuation of opioid therapy at this point might represent initiation of long-term opioid therapy, which should occur only as an intentional decision that benefits are likely to outweigh risks after informed discussion between the clinician and patient and as part of a comprehensive pain management approach.
- Clinicians seeing new patients already receiving opioids should establish treatment goals, including functional 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 patients who have low incomes, do not have health insurance, or have inadequate insurance.
- Clinicians should ensure that patients are aware of expected benefits of, common risks of, 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 (*155*). Detailed recommendations on diagnosis are provided in other guidelines (*156-159*). Evaluation should include a focused history, including history and characteristics of pain and potential contributing factors (e.g., function, work history and current work demands, psychosocial stressors, and sleep), and physical examination, 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) (*158,159*). For complex pain syndromes, consultation with a pain specialist can be considered to assist with diagnosis and management.

Diagnosis can help identify disease-specific interventions to reverse, ameliorate, or prevent worsening of pain and improve function (e.g., 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 severe mechanical or compressive pain) (*159*). The underlying mechanism for most pain syndromes has traditionally been categorized as neuropathic (e.g., diabetic neuropathy and postherpetic neuralgia) or nociceptive (e.g., osteoarthritis and muscular back pain). More recently, nociplastic pain has been suggested as a third, distinct category of pain with augmented central nervous system pain and sensory processing and altered pain modulation as experienced in conditions such as fibromyalgia (*160*). The diagnosis and pathophysiologic mechanism of pain have implications for symptomatic pain treatment with medication. For example, evidence is limited for improved pain or function, or evidence exists of worse outcomes, with long-term use of opioids for several chronic pain conditions for which opioids are commonly prescribed, such as osteoarthritis (*161*), nonspecific low back pain (*119,162*), headache (*152*), and fibromyalgia (*163,164*). For moderate to severe chronic back pain or hip or knee osteoarthritis pain, a nonopioid strategy starting with acetaminophen or NSAIDs results in improved pain intensity with fewer side effects compared with a strategy starting with opioids (*74*). Tricyclic antidepressants, SNRI antidepressants, selected anticonvulsants, or transdermal lidocaine are recommended for neuropathic pain syndromes (e.g., diabetic neuropathy or postherpetic neuralgia) (*156*).

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, considering patient-specific factors. For example, clinicians should consider fall risk when selecting and dosing potentially sedating medications (e.g., tricyclic antidepressants, anticonvulsants, and opioids) and should weigh benefits and risks of use, dosage, and duration of NSAIDs when treating older adults and patients with hypertension, renal insufficiency, heart failure, or those with risk for peptic ulcer disease or cardiovascular disease. NSAIDs are potentially inappropriate for use in older adults with chronic pain because of higher risk for adverse effects with prolonged use (*165*). Some guidelines recommend topical NSAIDs for localized osteoarthritis (e.g., knee osteoarthritis) over oral NSAIDs in patients aged ≥75 years to minimize systemic effects (*166*). (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 behavioral therapies (e.g., cognitive behavioral therapy and mindfulness-based stress reduction), can improve pain and function without risk for serious harms (*9*). High-quality evidence exists 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 (*9,167–170*). Previous guidelines have recommended aerobic, aquatic, or resistance exercises for persons with chronic pain, including osteoarthritis of the knee or hip, back pain, and fibromyalgia (*119,156,166,171*). Other noninvasive nonpharmacologic therapies that improve pain, function, or both for at least 1 month after delivery without apparent risk for serious harm include cognitive behavioral therapy 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, and qigong), massage, and acupuncture for neck pain; cognitive behavioral therapy, myofascial release massage, mindfulness practices, tai chi, qigong, acupuncture, and multidisciplinary rehabilitation for fibromyalgia; and spinal manipulation for tension headache (*9*). 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 (*172,173*). Exercise, mind-body interventions, and behavioral treatments (including cognitive behavioral therapy and mindfulness practices) can encourage active patient participation in the care plan and help address the effects of pain in the patient's life; these 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 (*9*). In addition, physical activity can provide additional health benefits, such as preventing or reducing symptoms of depression (*174*). 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 covered or fully covered by insurance (*43*). Access and cost can be barriers for patients, particularly persons who have low incomes, do not have health insurance or have inadequate insurance, have transportation challenges, or live in rural areas where services might not be available (*121*). Health insurers and health systems can improve pain management and reduce medication use and associated risks by increasing reimbursement for and access to noninvasive nonpharmacologic therapies with evidence for effectiveness (*9,43*). In addition, for many patients, aspects of these approaches can be used even when access to specialty care is limited. For example, previous guidelines have strongly recommended aerobic, aquatic, or resistance exercises for patients with osteoarthritis of the knee or hip (*166*) and maintenance of physical activity, including normal daily activities, for patients with low back pain (*158*). 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 those assigned to individual physiotherapy or muscle reconditioning sessions (*175*). 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 whose pain has 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 (*176*). In addition, primary care clinicians can integrate elements of psychosocial therapies such as cognitive behavioral therapy, which addresses psychosocial contributors to pain and improves function (*177*), by encouraging patients to take an active role in the care plan, supporting patients in engaging in activities such as exercise that are typically beneficial but that might initially be associated with fear of exacerbating pain (*159*), or providing education in relaxation techniques and coping strategies. In many locations, free or low-cost patient support, self-help, and educational community-based or employer-sponsored programs are available that can provide stress reduction and other mental health benefits. Clinicians should become 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 clinically significant psychological distress can be referred for treatment with a mental health specialist (e.g., psychologist, psychiatrist, or 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 comorbidities such as cardiovascular, renal, gastrointestinal, and liver disease. For example, NSAID use has been associated with serious gastrointestinal events and major coronary events (*8*). Increases in nonserious adverse events have been found with anticonvulsants pregabalin (blurred vision, cognitive effects, sedation, weight gain, dizziness, and peripheral edema) and gabapentin (blurred vision, cognitive effects, sedation, and weight gain), cannabis (nausea and dizziness), and SNRI antidepressants duloxetine (nausea and sedation) and milnacipran (nausea); dosage reductions reduced the risk for some adverse events with SNRI antidepressants (*8*). Clinicians should review FDA-approved labeling, including boxed warnings, before initiating treatment with any pharmacologic therapy.

For osteoarthritis, NSAIDs including topical NSAIDs and SNRI antidepressant duloxetine have small to moderate benefits for pain and function at short-term assessment (3–6 months), with intermediate-term (6–12 months) evidence for certain medications (celecoxib and duloxetine) and evidence that duloxetine is more effective in older (>65 years) than younger patients and in patients with knee osteoarthritis (*8*). Acetaminophen has limited evidence for effectiveness (*8*) and is no longer considered a first-line treatment for osteoarthritis (*161*). When patients have an insufficient response to nonpharmacologic interventions (e.g., 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 (*161*). In patients with osteoarthritis pain in multiple joints or incompletely controlled pain with topical NSAIDs, systemic NSAIDs or duloxetine can be used. However, systemic NSAIDs should be used at the lowest effective dosage and shortest duration needed because risks might increase with longer use and at higher dosages (*178*).

Oral NSAIDs should be used with caution, particularly in older persons and 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 inhibitors or NSAIDs with proton pump inhibitors can be used to minimize risk compared with risk with use of NSAIDs alone (*161*).

Moderate-quality evidence demonstrates small improvements in chronic low back pain with NSAIDs (*119*) and with duloxetine (*8*). When patients with low back pain have had an insufficient response to nonpharmacologic approaches such as exercise, clinicians can consider NSAIDs or duloxetine (*119*) for patients without contraindications.

For temporomandibular disorder pain that is not sufficiently improved with nonpharmacologic interventions, NSAIDs can be effective (*179,180*). Tricyclic, tetracyclic, and SNRI antidepressants; selected anticonvulsants; and capsaicin and lidocaine patches are recommended for neuropathic pain (*156*). However, evidence on topical lidocaine and capsaicin is limited (*8*). SNRI antidepressant duloxetine and anticonvulsants pregabalin, gabapentin, enacarbil, and oxcarbazepine are associated with small improvements in neuropathic pain (mainly diabetic neuropathy and postherpetic neuralgia) (*8*). Duloxetine and pregabalin are FDA-approved for the treatment of diabetic neuropathy, and pregabalin and gabapentin are FDA-approved for treatment of postherpetic neuralgia.

In patients with fibromyalgia, multiple medications are 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) (*8*). Tricyclic and SNRI antidepressants also can relieve fibromyalgia symptoms. Duloxetine, milnacipran, and pregabalin are FDA-approved for and are recommended for the treatment of fibromyalgia (*156*). Tricyclic antidepressant amitriptyline often is used and recommended for patients with fibromyalgia (*156*), although evidence for its effectiveness is limited (*8*). Because patients with chronic pain might experience concurrent depression (*181*) and depression can exacerbate physical symptoms including pain (*182*), patients with co-occurring pain and depression might be especially likely to benefit from antidepressant medication (see Recommendation 8).

Tricyclic antidepressants are potentially inappropriate for older adults (aged ≥65 years) because of their anticholinergic effects (*165*). Evidence on effectiveness of cannabis for painful conditions is limited and inconsistent across studies, and some studies have reported adverse events such as dizziness, nausea, and sedation (*8,183*).

## Opioid Medication for Subacute and Chronic Pain

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 (*7*). Compared with no opioid use, opioid use was associated with increased risk for opioid use disorder, overdose, all-cause deaths, fractures, falls, and myocardial infarction (*7*). Opioids also were associated with increased risk for discontinuation because of gastrointestinal adverse events, somnolence, dizziness, and pruritus (*7*). Compared with placebo, at short-term follow-up (1 to <6 months), opioids were associated with small mean improvements in pain intensity (mean difference: −0.79 on a 0–10 scale; 95% CI: −0.93 to −0.67; $I^2$: 71%) and function (*7*). Some evidence indicates that improvement in pain is reduced with longer duration of opioid therapy, from a mean improvement of 1 on a 0–10 scale at 1–3 months to approximately 0.5 at 3–6 months (*7*). No placebo-controlled trial evaluated effectiveness of opioids at intermediate (6 to <12 months) or long-term (≥12 months) follow-up (*7*). Compared with nonopioid treatments at short-term follow-up, there were no differences in mean pain improvement (mean difference: −0.29 on a 0–10 scale; 95% CI: −0.61 to 0.03) or functional improvement. No trials were identified that compared opioids with nonopioid therapies at intermediate- or long-term follow-up, with the exception of one trial that found stepped therapy starting with opioids to be associated with higher pain intensity than stepped therapy starting with nonopioids (4.0 versus 3.5; mean difference: 0.5; 95% CI: 0–1.0) at 12 months (*7,74*).

Clinical evidence reviews identified an observational study (*54*) finding long-term (>90 days' supply) opioid prescription to be associated with considerably increased risk for a new opioid use disorder diagnosis for all dosages of long-term (>90 days' supply) opioids prescribed compared with no opioids prescribed, with adjusted odds ratios of 15, 29, and 122 at low (1–36 MME/day), medium (36–120 MME/day), and high (≥120 MME/day) opioid dosages, respectively. Compared with no opioid use, opioid use was associated with increased risk for opioid use disorder, overdose, all-cause deaths, fractures, falls, and myocardial infarction (*7*).

Multiple experts from OWG stated that they appreciated this recommendation because of the importance of highlighting both pain and function, sharing realistic expectations with patients before initiating treatment, and paying attention to tapering and exit strategies. Although some experts reasoned 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 because 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 also is limited, these therapies also are associated with short-term benefits, no evidence exists 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 treatment 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.

Clinical evidence reviews found no instrument with high accuracy for predicting opioid-related harms, such as overdose or opioid use disorder (*7*). For clinicians, predicting whether benefits of opioids for chronic pain will outweigh risks of ongoing opioid treatment for individual patients can be challenging. Therefore, opioid therapy should only be initiated with consideration by the clinician and patient of an exit strategy that could be used if opioid therapy is unsuccessful in improving pain and pain-related function.

Before opioid therapy is initiated for subacute or chronic pain, clinicians should determine with patients how functional benefit will be evaluated and establish treatment goals. Some patients have reported treatment goals are effective in increasing motivation and functioning (*7*). Goals ideally include improvement in function (including social, emotional, and physical dimensions), pain, and quality of life. Goals can be tailored to specific 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 function, pain severity, and quality of life using tools such as the three-item PEG (Pain average, Interference with Enjoyment of life, and Interference with General activity) assessment scale (*184*) (see Recommendation 7). Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function (*185*). 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, and attending family events or recreational activities), and then use these goals in assessing benefits of opioid therapy and weighing benefits against risks of continued opioid therapy for individual patients (see Recommendation 7).

Patients with subacute pain might be at a particularly critical point, both for potential transition to chronic pain and potential transition to long-term opioid therapy. Clinicians should reevaluate patients with subacute pain and their treatment course, ensure that potentially reversible causes of ongoing pain are addressed, and optimize pain management as needed. For patients with subacute pain who started opioid therapy for acute pain and have been treated with opioid therapy for ≥30 days, clinicians should ensure that opioid prescribing for acute pain does not unintentionally become long-term opioid prescribing simply because medications are continued without reassessment. Continuation of opioid therapy at this point might represent initiation of long-term opioid therapy, which should occur only as an intentional decision that benefits are likely to outweigh risks after informed discussion between the clinician and patient and as part of a comprehensive pain management approach.

Clinicians seeing new patients already using opioid medication should establish treatment goals, including functional 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 (*7*), clinicians and patients who clearly document a treatment plan including specific functional goals in advance of prescribing will clarify expectations about 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 risks of, 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 important effects (*7*). The following elements are essential for communication and discussion with patients before starting opioid therapy:

- Review available low-cost options for pain management for all patients, and particularly for patients who have low incomes, do not have health insurance, or have inadequate insurance. Review considerations related to access to care because of 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 eliminated.
- Advise patients about serious adverse effects of opioids, including potentially fatal respiratory depression and development of a potentially serious opioid use disorder that can cause distress and inability to fulfill major 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. Prophylactic pharmacologic therapy (e.g., a stimulant laxative such as senna, with or without a stool softener) is usually needed to ensure regular bowel movements if opioids are taken regularly. Stool softeners or fiber laxatives without another laxative should be avoided.

- If formulations are prescribed that combine opioids with acetaminophen, advise patients of the risks for taking additional over-the-counter products containing acetaminophen.
- 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 the potential for workplace toxicology testing programs to detect therapeutic opioid use.
- 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 than prescribed or taking them more often).
- Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, nonprescribed drugs such as heroin, or other opioids.
- Discuss risks for household members and other persons 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 (*154*).
- Discuss the importance of periodic reassessment to ensure that opioids are helping to meet patient goals and, if opioids are not effective or are harmful, to allow opportunities for consideration of opioid tapering and dosage reduction or discontinuation and of additional nonpharmacologic or nonopioid pharmacologic treatment options.
- 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 PDMP 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 comanage medication therapy. Discuss the importance of reassessing medication use over time with both the patient and caregiver, as appropriate.

Because of the possibility that benefits of opioid therapy might diminish or that risks might become more prominent over time, clinicians should 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

Office-based interventional approaches, such as arthrocentesis and intra-articular glucocorticoid injection for pain associated with rheumatoid arthritis (*186*) or osteoarthritis (*187*) and subacromial corticosteroid injection for rotator cuff disease (*188*), can provide short-term improvement in pain and function to supplement or facilitate exercise, physical therapy, and other conservative approaches. Evidence is insufficient to determine the extent to which repeated glucocorticoid injection increases potential risks such as articular cartilage changes (in osteoarthritis) and sepsis (*187*).

Interventional pain management specialists offer additional interventions that can alleviate pain as part of a comprehensive pain management approach (*6*) for patients with indications including back pain, persistent pain after spinal surgery, neuropathic pain, and complex regional pain syndrome. Certain more common procedures include 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 and spinal cord stimulation). Descriptions of common interventional procedures are available (*6*). Level of evidence for effectiveness and risks varies by procedure, and additional research is needed to establish the clinical benefits as well as risks of specific interventional procedures for specific pain conditions (*6,189*) compared with risks of opioid pain medications and other pharmacologic therapies. Rare, serious adverse events have been reported with epidural injection (*190*). Interventional procedures should be performed by properly trained clinicians following meticulous infection control protocols. Clinicians can consult with a qualified pain management specialist who is well versed in benefits and risks of diagnostic and therapeutic options to determine potential appropriateness of specific interventional procedures for their patients' indications and clinical circumstances.

### Multimodal Therapy for Subacute and Chronic Pain

Integrated pain management requires coordination of medical, psychological, and social aspects of health care and includes primary care, mental and behavioral health care, and specialist services when needed (*191*). Multimodal therapies and multidisciplinary biopsychosocial rehabilitation (e.g., combining 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 also can provide synergistic benefits when nonopioid or opioid pain medications are used (*6*). 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 in abilities to access multimodal care exist (*6*). Evidence exists that less-intensive multidisciplinary rehabilitation can be similarly effective to high-intensity multidisciplinary rehabilitation (*9*). 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 comorbidities and benefit-to-risk ratios in individual patients, combinations of medications (e.g., two nonopioid medications with different mechanisms of action or a nonopioid with an opioid medication) also might be used. In some cases, medication combinations might provide complementary or synergistic benefits and facilitate lower dosing of individual medications, as has been demonstrated in trials of patients with neuropathic pain (*7*). However, this approach should be used with caution 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 for overdose compared with either medication alone (*7*).

## Selecting Opioids and Determining Opioid Dosages

### Recommendation 3

**When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and 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. FDA has noted that some ER/LA opioids should be considered only for patients who have received certain dosages of 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.
- 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. Clinical evidence reviews found that 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 five 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 (*7*). A fair-quality study demonstrated 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 (*7,192*). 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 risk for opioid use disorder (*7*).

In 2014, 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 (*49*). FDA 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 (*193*). Time-scheduled opioid use can be associated with greater total average daily opioid dosage compared with intermittent, as-needed opioid use (*194*). Technologies have been used 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. FDA guidance for industry on evaluation and labeling of these "abuse-deterrent" opioids (*195*) indicates that these technologies, although they are expected to make manipulation of opioids more difficult or reduce the potent effects of manipulation, 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, opioid use disorder, or overdose (*7*). Experts from OWG agreed with the recommendation for clinicians to initiate opioid treatment with immediate-release opioids instead of with ER/LA opioids and said they appreciated discussion of the lack of evidence for "abuse-deterrent" formulations.

In comparing different ER/LA formulations, 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 for overdose or all-cause deaths versus morphine and one cohort study of U.S. Department of Veterans Affairs patients finding methadone to be associated with decreased risk (*7*). Methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for pain (*196*). 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 (*197–199*). In regard to other ER/LA opioid formulations, the absorption and pharmacodynamics of transdermal fentanyl are complex, with gradually increasing serum concentration during the first part of the 72-hour dosing interval, and variable absorption affected by 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. Because of the longer half-life and longer duration of effects (e.g., respiratory depression) of ER/LA opioids (e.g., methadone, fentanyl patches, or extended-release versions of 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 (*193*). 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 in certain situations clinicians might need to prescribe immediate-release and ER/LA opioids together (e.g., when transitioning patients from ER/LA opioids to immediate-release opioids by temporarily using lower dosages of both, for temporary postoperative use of short-term opioids in a patient already receiving ER/LA opioids, or in patients with opioid use disorder treated and stabilized on methadone who need short-acting opioids for acute pain), clinicians should consider the potential for increased overdose risk and use caution when prescribing immediate-release opioids in combination with ER/LA opioids.

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 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 (*200*). Because dosing effects of transdermal fentanyl often are misunderstood by both clinicians and patients, only clinicians who are familiar with its dosing and absorption properties of and are prepared to educate their patients about its use should consider prescribing transdermal fentanyl.

## Recommendation 4

**When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage. 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

- 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. 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. Therefore, the recommendation language emphasizes that clinicians should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients rather than emphasizing a single specific numeric threshold. 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).

- When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage.
- For patients not already taking opioids, the lowest effective dose can be determined using product labeling as a starting point with calibration as needed based on the severity of pain and 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 5–10 MME or a daily dosage of 20–30 MME/day. A listing of common opioid medications and their doses in MME equivalents is provided (Table).
- 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. 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.
- Additional dosage increases beyond 50 MME/day are progressively more likely to yield diminishing returns in benefits for pain and function relative to risks to patients as dosage increases further. Clinicians should carefully evaluate a decision to further increase dosage on the basis of 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.

### Supporting Rationale

Benefits of high-dose opioids for pain are not well established. Few trials evaluated opioid dosages of ≥90 MME/day (*7*). Opioid dosages of 50–90 MME/day were associated with a minimally greater (below the threshold for small) improvement in mean pain intensity compared with dosages of <50 MME/day (mean difference: −0.26; 95% CI: −0.57 to −0.02); there was no difference in mean improvement in function (*7*). Analyses of placebo-controlled trials also found some evidence of a plateauing effect at ≥50 mg MME/day (*7*). One trial of more liberal dose escalation compared with maintenance of current dosage found no difference in outcomes related to pain or function (*7*).

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 (*201*). One cohort study from the clinical evidence reviews found higher dosages of opioids were associated with increased risk for all-cause deaths; one cohort study found modest associations between higher dose of long-term opioid and increased risk for falls and major trauma; one case-control study found opioid dosages of >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 dosages of >20 MME/day; and cohort studies found association between higher opioid dose and risk for various endocrinological adverse events (*7*). Patients on higher doses reported reliance on opioids despite ambivalence about their benefits (*7*).

Four observational studies identified in the clinical evidence reviews consistently found an association between higher doses of long-term opioids and risk for overdose or overdose death (*7*). Opioid dosages for chronic pain of 50 to <100 MME/day in observational studies have been associated with increased risks for opioid overdose by factors of 1.9–4.6 compared with dosages of 1 to <20 MME/day, and dosages of ≥100 MME/day were found to be associated with increased risks for overdose 2.0–8.9 times the risk at 1 to <20 MME/day, after adjusting for confounders on the basis of demographics, comorbidities, concomitant medications, and other factors (*55,202,203*). When opioids are prescribed for acute pain, similar associations have been found, with dosages of 50 to <100 MME/day associated with 4.73 times the risk for overdose and dosages of ≥100 MME/day associated with 6.64 times the risk, compared with dosages of 1 to <20 MME/day (*55*). The MME cut points in these studies (e.g., 20 MME, 50 MME, and 100 MME) were selected by the authors for research purposes, and whereas 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 daily opioid dosage among patients who died from opioid overdose was 98 MME (median: 60 MME), compared with mean prescribed daily opioid dosage of 48 MME (median: 25 MME) among patients not experiencing fatal overdose (*204*). A narrative review conducted by FDA staff concluded that, although there is not a single dosage threshold below which overdose risk is eliminated (*201*), the studies included in the review indicated an increasing risk for serious adverse health outcomes, including misuse, overdose, and death associated with increasing opioid dose. These studies examined dose-response risk for 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 (*205*).

Multiple experts from OWG expressed concern that including specific dosage thresholds in a main recommendation statement would emphasize them as authoritative absolutes and would lead to noncollaborative tapers or other potentially harmful consequences. Experts also noted the lack of a single standard formula for calculating MMEs (*206*). However, experts agreed there is a need for thresholds as benchmarks and suggested including them in the supporting text after 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.

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 effective dose can be determined using product labeling as a starting point with calibration as needed on the basis of the severity of pain and 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 5–10 MME or a daily dosage of 20–30 MME/day. A listing of common opioid medications and their doses in MME equivalents is provided (Table). For example, a label for hydrocodone bitartrate (5 mg) and acetaminophen (300 mg) (*207*) states that the usual adult dosage is one or two tablets every 4–6 hours as needed for pain, and the total daily dosage should not exceed eight tablets. Clinicians should use additional caution when initiating opioids for patients aged ≥65 years and 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/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.

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 evidence to recommend specific intervals for dosage titration is limited, 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 because of the risks for respiratory depression. In the context of long-term opioid use, when dosage is increased, clinicians should reevaluate 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, considering that dosage increases to >50 MME/day are unlikely to provide substantially improved pain control for most patients while overdose risk increases with dosage, and carefully reassess evidence of 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 the patient and the patient's household members (see Recommendation 8).

Additional dosage increases beyond 50 MME/day are progressively more likely to yield diminishing returns in benefits for pain and function relative to risks to patients. Clinicians should carefully evaluate a decision to increase dosage after an 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.

Certain 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 the increase is indicated and appropriate (*208*). Clinicians should be aware of policies related to MME thresholds and associated clinical protocols established by their states.

## Recommendation 5

**For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage. If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy. If benefits do not outweigh risks 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 circumstances of the patient, 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 rapidly reduce opioid dosages from higher dosages (recommendation category: B; evidence type: 4).**

### Implementation Considerations

- Clinicians should carefully weigh both the benefits and risks of continuing opioid medications and the benefits and risks of tapering opioids.
- If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy.
- When benefits (including avoiding risks of tapering) do not outweigh risks of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to a reduced opioid dosage or, if warranted based on the individual clinical circumstances of the patient, appropriately taper and discontinue opioid therapy.
- In situations where benefits and risks of continuing opioids are considered to be close or unclear, shared decision-making with patients is particularly important.
- At times, clinicians and patients might not be able to agree on whether or not tapering is necessary. When patients and clinicians are unable to arrive at a consensus on the assessment of benefits and risks, clinicians should acknowledge this discordance, express empathy, and seek to implement treatment changes in a patient-centered manner while avoiding patient abandonment.
- 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 and 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 might be warranted.
- Clinicians should follow up frequently (at least monthly) with patients engaging in opioid tapering. Team members (e.g., nurses, pharmacists, and behavioral health professionals) can support the clinician and patient during the ongoing taper process through telephone contact, telehealth visits, or face-to-face visits.
- 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.
- Longer duration of previous opioid therapy might require a longer taper. For patients who have taken opioids long-term (e.g., for ≥1 year), tapers can be completed over several months to years depending on the opioid dosage and should be individualized based on patient goals and concerns.
- When patients have been taking opioids for longer durations (e.g., for ≥1 year), tapers of 10% per month or slower are likely to be better tolerated than more rapid tapers.
- For patients struggling to tolerate a taper, clinicians should maximize nonopioid treatments for pain and should address behavioral distress.
- Clinically 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 as patients reach low dosages.
- Before reversing a taper, clinicians should carefully assess and discuss with the patient the benefits and risks of increasing opioid dosage.
- Goals of the taper might vary (e.g., some patients might achieve discontinuation whereas others might attain a reduced dosage at which functional benefits outweigh risks). If the clinician has determined with the patient that the ultimate goal of tapering is discontinuing opioids, after the smallest available dose is reached the interval between doses can be extended and opioids can be stopped when taken less frequently than once a day.
- Clinicians should access appropriate expertise if considering tapering opioids during pregnancy because of possible risks to the pregnant patient and the fetus if the patient goes into withdrawal.
- Clinicians should advise patients of an increased risk for overdose on abrupt return to a previously prescribed higher dose because of loss of opioid tolerance, provide opioid overdose education, and offer naloxone.
- Clinicians should remain alert to signs of and screen for 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 comorbidities.
- 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.
- Payers, health systems, and state medical boards should not use this clinical practice guideline to set rigid standards or performance incentives 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; and should ensure that policies do not penalize clinicians for accepting new patients who are using prescribed opioids for chronic pain, including those receiving high dosages of opioids, or for refraining from rapidly tapering patients prescribed long-term opioid medications.
- Although Recommendation 5 specifically refers to patients using long-term opioid therapy for subacute or chronic pain, many of the principles in these implementation considerations and supporting rationale, including communication with patients, pain management, behavioral support, and slower taper rates,

also are relevant when discontinuing opioids in patients who have received them for shorter durations (see Recommendations 6 and 7).

### Supporting Rationale

Patients receiving long-term, high-dosage opioid therapy for chronic pain are at increased risk for adverse events including overdose death (*55,72,202,203,209*). However, discontinuation of long-term, high-dosage opioid therapy has been associated with adverse events including mental health crisis, overdose events, and overdose death (*71–73,210,211*). In addition, opioid tapering has been found to be associated with subsequent termination of care (*212*). One study found that whereas sustained opioid therapy discontinuation (i.e., opioid discontinuation for at least 3 months) was associated with an approximately 50% reduction in risk for overdose, dose variability was a risk factor for opioid overdose (*213*). In another study, discontinuation of long-term, high-dosage opioid therapy was associated with increased risk for suicide but with reduced risk for overdose when compared with stable or increasing dosage (*211*). Both starting and stopping opioids were associated with overdose or suicide risk in another study; risk associated with stopping opioids was increased when patients had received opioids for longer durations. Death rates for overdose or suicide in one study increased immediately after starting or stopping treatment with opioids, with the incidence decreasing over approximately 3–12 months (*214*) in one study and persisting over 2 years in another study (*215*). In observational studies evaluating outcomes related to heroin use after discontinuation of prescription opioids, one study found that heroin use was associated with discontinuation of long-term opioid use (*216*); another study found that among persons experiencing heroin overdose, prescription opioid use in the past 12 months was common but discontinuation of long-term opioid use was uncommon (*217*).

Discontinuation of opioids has been associated with greater risks when it occurs over shorter periods. 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 (*68*). One observational study found that, among adults prescribed stable higher opioid dosages (mean: ≥50 MME/day) long-term, increasing maximum monthly dose reduction rate by 10% was associated with an adjusted incidence rate ratio of 1.09 for overdose (95% CI: 1.07–1.11) and 1.18 for mental health crisis (95% CI: 1.14–1.21) (*210*). Another study of patients on long-term, high-dosage (≥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 for opioid-related emergency department visits or hospitalizations (*71*). The clinical evidence reviews did not find studies comparing different rates of opioid tapering; however, 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 with usual care, with effects persisting at 34-week follow-up (*7*). A systematic review (*218*) found that, among studies rated as good or fair quality, when opioids were tapered after 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 medications as well as practices including behavioral support, integration of nonpharmacologic pain management, and slower tapers might improve outcomes.

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

## Determining Whether, When, and How to Taper Opioids

The benefits and risks of opioid therapy change over time and should be reevaluated 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 or unclear, shared decision-making with patients is particularly important. At times, clinicians and patients might not be able to agree on whether tapering is necessary. When patients and clinicians are unable to arrive at a consensus on the assessment of benefits and risks, clinicians should acknowledge this discordance, express empathy, and seek to implement treatment changes in a patient-centered manner while avoiding patient abandonment. Unless there is a life-threatening issue such as warning signs of an imminent overdose, the benefits of rapidly tapering or abruptly discontinuing opioids are unlikely to outweigh the substantial risks of these practices (*71,219*). However, after slow, voluntary reduction of long-term opioid dosages, patients might experience improvements in function, quality of life, anxiety, and mood without worsening pain or with decreased pain levels (*218*). Clinicians and patients should consider whether opioids continue to meet treatment goals, including functional 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 might be warranted (i.e., when benefits of opioids outweigh risks) (*66,219*). Clinicians should access appropriate expertise if considering tapering opioids during pregnancy because of possible risk to the pregnant patient and the fetus if the patient goes into withdrawal. For pregnant persons 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) (*220,221*).

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). Benzodiazepines should be tapered gradually because of risks (anxiety, hallucinations, seizures, delirium tremens, and, rarely, death) of benzodiazepine withdrawal (*222,223*). Patients who are not taking prescribed opioids (e.g., 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 (*219*), clinicians should consider tapering to a reduced opioid dosage or tapering and discontinuing opioid therapy and discuss these approaches with patients before initiating changes when

- the patient requests dosage reduction or discontinuation,
- pain improves and might indicate resolution of an underlying cause,
- 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 the benefit-risk balance is unclear (e.g., decreased positive effects because of tolerance and symptoms such as reduced focus or memory that might be due to opioids),
- the patient is receiving higher opioid dosages without evidence of benefit from the higher dosage,
- the patient experiences side effects that diminish quality of life or impair function,
- evidence of opioid misuse exists,
- 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 (e.g., confusion, sedation, or slurred speech), or
- the patient is receiving medications (e.g., benzodiazepines) or has medical conditions (e.g., sleep apnea, liver disease, kidney disease, or fall risk) that increase risk for adverse outcomes.

For patients already taking opioids long term (both established patients and patients transferring from other clinicians), the possibility of opioid dosage reduction might provoke substantial anxiety. In addition, tapering opioids after years of taking them can be especially challenging because of physical and psychological dependence. However, patients should be offered the opportunity to reevaluate their continued use of opioids. Clinicians should review benefits and risks of continued opioid therapy with empathy.

Whenever possible, clinicians should collaborate with patients and share decision-making about whether and how to taper opioids. Clinicians should review benefits and risks of opioid therapy with the patient and decide whether tapering is appropriate for the patient. If the existing opioid regimen does not put the patient at imminent risk for overdose or other injury, tapering does not need to occur immediately, and clinicians can take time to reach agreement with patients (*224*). For patients who agree to taper opioids to lower dosages, clinicians should collaborate with the patient on a tapering plan. Open discussion between the clinician and patient should take place, whether the goal of the taper is stopping opioids or reducing opioids to a point where benefits outweigh risks; the goal will depend on the patient's circumstances and an individualized assessment of benefits and risks. Tapering is more likely to be successful when patients collaborate in the taper (*224*). Clinicians can discuss with patients the patient's perceptions of benefits, risks, and adverse effects of continued opioid therapy; include patient concerns in taper planning; and include patients in making decisions such as which medication will be decreased first (e.g., in patients prescribed more than one opioid) and how quickly tapering will occur.

### Providing Advice to Patients Before Tapering

Clinicians should advise patients that overall, after voluntary reduction of long-term opioid dosages, most patients report stable or improved function, anxiety, and mood without worsening pain or with decreased pain levels (*66,218,225–228*). However, other patients report insomnia, anxiety, depression, and increased pain, particularly in the short term (*66,225,227,229,230*). Increased pain might be related to hyperalgesia or opioid withdrawal and can be prolonged in some patients (*229*). Patients can be counseled that worsening of pain is a frequent symptom of opioid withdrawal that tends to diminish over time (*219*). Clinicians should advise patients about the increased risk for overdose with abrupt return to a previously prescribed higher dosage because of loss of opioid tolerance and warn of a risk for overdose if the patient returns to their original dosage (*219*). 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. Nonpharmacologic and nonopioid treatments should be integrated into patients' pain management plans after an individualized assessment of benefits and risks that considers 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 (*218*) and strengthen the therapeutic relationship between the clinician and patient. Whether patients are agreeing to taper to lower opioid dosages or remaining on higher opioid dosages, clinicians should work with them to establish functional goals 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 (*218*), strengthen the therapeutic relationship between the clinician and patient, and improve the likelihood of positive tapering outcomes (*228*). Mental health comorbidities including depression and anxiety are common in patients with painful conditions, especially those receiving long-term opioid therapy (*231*). Depressive symptoms predict taper dropout (*225,226*). Primary care clinicians should collaborate with mental health specialists and with other specialty clinicians as needed to optimize nonopioid pain management (see Recommendation 2) and provide psychosocial support for patients who have 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 risk for suicide or with suicidal ideation (*219*). Clinicians should remain alert to signs of and screen for 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 comorbidities. Successful tapering studies have used at least weekly follow-up (*218*), and clinicians should follow up frequently (at least monthly) with patients engaging in opioid tapering. Team members (e.g., nurses, pharmacists, and behavioral health professionals) can support the clinician and patient during the ongoing taper process through telephone contact, telehealth visits, or face-to-face visits. Clinicians can acknowledge patient fears about tapering (*232*), ask how they can support the patient (*232*), and make sure patients receive appropriate and accessible psychosocial support (*228*). Many patients fear withdrawal symptoms, pain, or abandonment (*233*), and clinicians can help patients by telling them what to expect (e.g., the rate will be kept slow to minimize withdrawal symptoms and pain might worsen at first but usually improves over time) and that they will be supporting them through the process.

### Tapering Rate

Evidence to support specific tapering rates is limited. The rate of tapering should be individualized based on the patient's clinical situation. 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 when patients have been taking opioids for longer durations (e.g., ≥1 year) (*219*). When patients have taken opioids for shorter durations (e.g., weeks to months rather than years), 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 less likely to trigger withdrawal (*225*) and can be successful for some patients. For patients struggling to tolerate a taper, clinicians should maximize nonopioid treatments for pain and should address behavioral distress (*234*). Clinically 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 as patients reach low dosages to allow gradual accommodation to lower opioid dosages and development of new skills for nonopioid management of pain and emotional distress. Before reversing a taper, clinicians should carefully assess and discuss with patients benefits and risks of increasing opioid dosage. If the clinician and patient have determined that the goal is discontinuing opioids, after the smallest available dose is reached, the interval between doses can be extended and opioids can 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) (*219*). 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 rapidly reduce opioid dosages from higher dosages. Sudden discontinuation might precipitate substantial opioid withdrawal (*71*). Rapid tapering or sudden discontinuation of opioids in physically dependent patients also can increase risks for psychological distress and opioid-related emergency department visits and hospitalizations (*68,71*). Ultrarapid detoxification under anesthesia is associated with substantial risks, including death, and should not be used (*235*).

### 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 (*232*). These include alpha-2 agonists for the management of autonomic signs and symptoms (e.g., sweating and tachycardia). Alpha-2 agonists clonidine and lofexidine are more effective than placebo in reducing severity of withdrawal (*236*) from heroin or methadone in the context of abrupt (not gradual) discontinuation. Similar research could not be found on clonidine and lofexidine in patients tapering from long-term opioid treatment for pain (*225*); however, alpha-2 agonist tizanidine has been used to help taper patients from long-term, high-dosage opioids for chronic pain (*230*). Other medications addressing specific symptoms (NSAIDs, acetaminophen, or topical menthol or 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) also have been used (*232*).

### Challenges to Tapering

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* (DSM-5) criteria and, if criteria for opioid use disorder are met, offered evidence-based medication treatment (see Recommendation 12) and naloxone for opioid

overdose reversal (see Recommendation 8).

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 (*219,237,238*). Buprenorphine is a partial agonist opioid that can treat pain and opioid use disorder (*239*) and has other properties that might be helpful (*155*), including less respiratory depression (*205*) and overdose risk than other opioids (*155,237*). Although 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 (e.g., full agonist opioids, benzodiazepines, or alcohol) (*240*). A specialty clinic offering opioid tapering services for patients receiving high-dosage opioids (defined in this study as ≥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 (*230*). Different buprenorphine products, available at different formulations and doses, are approved for the treatment of pain and for the treatment of opioid use disorder. Although prescription of buprenorphine for treatment of opioid use disorder requires the clinician to have a waiver from SAMHSA (see Recommendation 12), prescription of buprenorphine for treatment of chronic pain does not require a waiver (*237*).

To avoid precipitating withdrawal, transitioning any patient taking full agonist opioids to buprenorphine requires specific timing of the initial buprenorphine dose (*219*) (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 (*219*). To do this, experts have advised that clinicians and patients should wait at least 8–12 hours after the last dose of short-acting full agonist opioids and longer after 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, and longer for methadone) before the first dose of buprenorphine is administered (*229*). As an alternative for patients not yet in opioid withdrawal, certain studies have described low dose initiation of buprenorphine to allow for initiation of buprenorphine in patients receiving full agonist opioids for acute or chronic pain (*241*). SAMHSA's Providers Clinical Support System (https://pcssnow.org ) offers training, technical assistance, and mentors to assist clinicians who are unfamiliar with initiation of buprenorphine and have additional questions about the diagnosis and treatment of opioid use disorder. 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 (*242*), dosing of buprenorphine for pain is typically multiple times daily rather than once-a-day dosing as done for the treatment of opioid use disorder (*229*).

### Continuing High-Dosage Opioids

Clinicians should closely monitor patients who are unable to taper and who continue on high-dosage 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 (*224*).

Management of chronic pain with opioids can be challenging, as can management of opioid discontinuation (*67*). However, clinicians have a responsibility to provide or arrange for coordinated management of patients' pain and opioid-related challenges. Payers and health systems should not use this clinical practice guideline to set rigid standards related to dosage 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, do not penalize clinicians for accepting new patients who are receiving opioids for chronic pain, and do not provide incentives to clinicians to implement rapid tapering. Patients prescribed opioids but unable to access ongoing care (*243*) might be at risk for abrupt opioid discontinuation and might miss opportunities to receive life-saving interventions, including monitoring for and management of mental health and substance use comorbidities.

## Deciding Duration of Initial Opioid Prescription and Conducting Follow-Up

### Recommendation 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 to the patient's clinical circumstances.
- 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 (on the basis of actual use and refills and on consensus).
- To minimize unintended effects on patients, clinicians, practices, and health systems should have mechanisms in place for the subset of patients who experience severe acute pain that continues longer than the expected duration. These mechanisms should allow for timely reevaluation to confirm or revise the initial diagnosis and adjust pain management accordingly. Clinicians, practices, and health systems can help minimize disparities in access to and affordability of care and refills by ensuring all patients can obtain and afford additional evaluation and treatment, as needed.
- 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 ≥1 month, clinicians should ensure that potentially reversible causes of chronic pain are addressed and that opioid prescribing for acute pain does not unintentionally become long-term opioid therapy simply because medications are continued without reassessment. Continuation of opioid therapy at this point might represent initiation of long-term opioid therapy, which should occur only as an intentional decision that benefits are likely to outweigh risks after discussion between the clinician and patient and as part of a comprehensive pain management approach. Clinicians should refer to recommendations on subacute and chronic pain for initiation (Recommendation 2), follow-up (Recommendation 7), and tapering (Recommendation 5) of ongoing opioid therapy.
- If patients already receiving long-term opioid therapy 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 used continuously (around the clock) for more than a few days for acute pain, clinicians should prescribe a brief taper to minimize withdrawal symptoms on discontinuation of opioids.
- If a taper is needed, 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 before hospital discharge and with clinicians coordinating the patient's care as an outpatient. (See Recommendation 5 for tapering considerations when patients have taken opioids continuously for >1 month.)

### Supporting Rationale

Data suggest that pain improves within days for many patients with common types of acute pain in primary care or emergency department settings. 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 (*244*), suggesting that in most cases, clinicians considered an initial opioid prescription of 4–7 days' duration sufficient. Some patients (17.8%; range: 11.7%–30.0% depending on the acute pain condition) obtained at least one refill within 30 days after their initial opioid prescription, suggesting that although these durations might have been sufficient or more than necessary for most patients, variation across diagnoses and among patients in time to recovery is likely. In an older study of the course of acute low back pain (not associated with malignancies, infections, spondyloarthropathies, fractures, or neurologic signs) in a primary care setting, a large decrease in pain occurred until the fourth day after treatment with paracetamol, with smaller decreases thereafter (*245*). A more recent single-center survey of patients prescribed opioids for acute pain on emergency department discharge (*246*) found that patients taking opioids continued them for a median of 4 days (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 days (IQR: 4–8 days) for back pain and fractures, 2 days (IQR: 1–5 days) for renal colic, 5.5 days (IQR: 4–7 days) for musculoskeletal injury, and 3 days (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 similarly found most (68%) total prescribed opioids were unused, and the quantity of 5-mg morphine tablets to prescribe to adequately supply 80% of the patients with the amount of opioids they used was 20 tablets for musculoskeletal pain, 30 for fracture, 15 for renal colic or abdominal pain, and 20 for other pain conditions (*247*).

Since 2017, multiple studies 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 reductions in satisfaction with pain management (*77–79*). One study found that, after five common surgical procedures, median opioid consumption was three 5-mg 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%–56% of pills prescribed remaining unused (*248*). Evidence exists of variation in opioid needs across patients undergoing the same procedures attributable to factors including pain at discharge and previous opioid use (*249*). One study found that, although a majority of patients used no or few (>0 to <50 MME during their entire postoperative course) opioids, some patients required opioids for up to 15 days after surgery (*250*).

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-dependent effects (*63,75,141,244,251,252*). Opioids prescribed for surgery and other acute pain conditions that go unused are a potential source for misuse and diversion (*249,253–255*). In addition, sudden discontinuation of opioids might result in clinically significant opioid withdrawal (*71*). 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 and limit unused opioids. Certain circumstances (e.g., severe traumatic injuries) might require use of opioids for durations of >7 days. Durations should be individualized based on the patient's clinical circumstances.

When patients are discharged from the hospital after surgery, the course and dosage of any opioid medications administered during hospitalization and before discharge can help predict ongoing pain management needs (*150,256,257*). For postoperative pain, procedure-specific opioid prescribing recommendations are available with ranges for amounts of opioids needed (on the basis of use and refills and on consensus) (*149,151,250*).

Clinicians should generally not prescribe additional opioids to patients just in case pain continues longer than expected. However, if pain continues longer than expected, some patients might face challenges in successfully navigating the health care system (e.g., clinician and pharmacy contact, transportation, and 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 for the subset of patients who experience severe acute pain that continues longer than the expected duration. These mechanisms should allow for timely reevaluation to confirm or revise the initial diagnosis and adjust pain management accordingly. In particular, clinicians, practices, and health systems should ensure all patients can obtain and afford additional evaluation and treatment as needed to minimize disparities in 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. If opioids are continued for ≥1 month, clinicians should ensure that potentially reversible causes of chronic pain are addressed and that opioid prescribing for acute pain does not unintentionally become long-term opioid therapy simply because medications are continued without reassessment. Continuation of opioid therapy at this point might represent initiation of long-term opioid therapy, which should occur only as an intentional decision that benefits are likely to outweigh risks after discussion between the clinician and patient and as part of a comprehensive pain management approach. Clinicians should refer to recommendations on subacute and chronic pain for initiation (Recommendation 2), follow-up (Recommendation 7), and tapering (Recommendation 5) of ongoing opioid therapy. 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 used continuously (around the clock) for more than a few days for acute pain, clinicians should prescribe a brief 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 >3 days but for <1 week, clinicians can consider reducing the daily dosage to 50% for 2 days to ameliorate withdrawal symptoms when discontinuing opioids. When patients have taken opioids continuously for ≥1 week but <1 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) (*256,257*). When patients are discharged from the hospital after surgery, opioid dosages needed during hospitalization and before discharge can help predict tapering needs to prevent withdrawal symptoms (*150,256,257*). Tapering plans should be discussed with the patient before discharge and with clinicians coordinating the patient's care as an outpatient. (See Recommendation 5 for tapering considerations when patients have taken opioids continuously for >1 month.)

## Recommendation 7

**Clinicians should evaluate benefits and risks with patients within 1–4 weeks of starting opioid therapy for subacute or chronic pain or of dosage escalation. Clinicians should regularly reevaluate benefits and risks of continued opioid therapy with patients (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 1–4 weeks of starting long-term opioid therapy or of dosage escalation.
- Clinicians should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased, because of the increased risk for overdose within the first 2 weeks of treatment, or when total daily opioid dosage is ≥50 MME/day. (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 (every 2–3 days for the first week) should be strongly considered when starting or increasing the dosage of methadone, because of 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 of <50 MME/day.
- Clinicians should follow up with and evaluate patients with subacute pain who started opioid therapy for acute pain and have been treated with opioid therapy for 30 days to reassess the patient's pain, function, and treatment course; ensure that potentially reversible causes of chronic pain are addressed; and prevent unintentional initiation of long-term opioid therapy. Continuation of opioid therapy at this point might represent initiation of long-term opioid therapy, which should occur only as an intentional decision that benefits are likely to outweigh risks after discussion between the clinician and patient and as part of a comprehensive pain management approach (see Recommendation 2).
- 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, with a suggested interval of every 3 months or more frequently for most patients.
- Clinicians seeing new patients already receiving opioids should establish treatment goals, including functional goals, for continued opioid therapy (see Recommendation 2).
- Clinicians should reevaluate 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. Clinicians should regularly screen all patients for these conditions, which can change during the course of treatment (see Recommendation 8).
- Clinicians, practices, and health systems can help minimize unintended effects on patients by ensuring 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), or for patients for whom in-person follow-up visits are challenging (e.g., frail patients), follow-up assessments that allow the clinician to communicate with and observe the patient through telehealth modalities might 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, and determine 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 comorbidities is optimized.
- Clinicians should ask patients about their preferences for continuing opioids, considering 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 before initiation of opioid therapy; if patients are taking higher-risk regimens [e.g., dosages of ≥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 taper and reduce opioid dosage or taper and discontinue opioids when possible (see from Recommendation 5).
- Clinicians should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).

### Supporting Rationale

Although clinical evidence reviews did not find studies evaluating the effectiveness of more frequent monitoring intervals (*7*), they identified an observational study (*54*) that found risk for opioid use disorder was associated with continuing opioid therapy for ≥3 months. The reviews also identified a study that found risk for overdose associated with ER/LA opioids might be particularly high during the first 2 weeks of treatment (*192*). Another study found the first 3 months after opioid initiation to be a period of higher risk for opioid overdose (*214*). Patients who do not have pain relief with opioids at 1 month are unlikely to experience pain relief with opioids at 6 months (*258*). 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, including functional goals, and minimize risks of long-term opioid use by tapering and discontinuing opioids among patients not receiving a clear benefit from these medications. In addition, evaluation within the first 3 months might provide opportunities to identify and mitigate risks for opioid use disorder and overdose.

Experts from OWG noted that although little evidence exists for specific follow-up time frames, the recommendation was reasonable and reflects common practice and therefore supported the recommendation. 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., copays) could have consequences when recommending frequent visits and should be considered.

Clinicians should evaluate patients to assess benefits and risks of opioids within 1–4 weeks of starting long-term opioid therapy or of dosage escalation. Clinicians should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased, because of the increased risk for overdose within the first 2 weeks of treatment (*192*), or when total daily opioid dosage is ≥50 MME/day, because the 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 (every 2–3 days for the first week) should be strongly considered when starting or increasing the dosage of methadone because of 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 of <50 MME/day.

Patients who started opioid therapy for acute pain and are continuing to receive opioids for subacute pain might be at a particularly critical point for potential transition to chronic pain and potential transition to long-term opioid therapy. Clinicians should follow up with and evaluate patients with subacute pain who have been treated with opioid therapy for 30 days. Clinicians should ensure that opioid prescribing for acute pain does not unintentionally become long-term opioid therapy simply because medications are continued without reassessment, but only as an intentional decision that benefits are likely to outweigh risks after discussion between the clinician and patient. Clinicians should reassess the patient's pain, function, and treatment course; ensure that potentially reversible causes of chronic pain are addressed; and optimize pain management as needed (see Recommendation 2).

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 1–3 months than at 3–6 months (*7*). A cohort study found an association between longer duration of therapy and increased risk for new-onset depression (*7*). 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, with a suggested interval of every 3 months or more frequently. Clinicians seeing new patients already receiving opioids should establish treatment goals, including functional goals, for continued opioid therapy (see Recommendation 2). Clinicians should reevaluate 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. Clinicians should regularly screen all patients for these conditions, which can change during the course of treatment (see Recommendation 8). Clinicians, practices, and health systems can help minimize unintended effects on patients by ensuring all patients can access and afford follow-up evaluation (*86*). In addition, policymakers can consider evidence-based methods of minimizing barriers to care (e.g., paid sick leave) (*259*). 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), or for patients for whom in-person follow-up visits are challenging (e.g., frail patients), follow-up assessments that allow the clinician to communicate with and observe the patient through telehealth modalities might be conducted when available.

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; determine 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, and social or family problems related to opioid use); determine whether benefits of opioids continue to outweigh risks; and determine 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) or by using tools such as the three-item PEG assessment scale *(184)*; clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function *(185)*. Clinicians also should ask patients about common adverse effects such as constipation and drowsiness (see Recommendation 2) and should ask about and assess 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, or work, social, or family problems related to opioid use). Clinicians can use validated screening tools such as the Drug Abuse Screening Test (DAST) *(260)*, the Tobacco, Alcohol, Prescription medication, and other Substance use Tool (TAPS) *(261)*, and the three-question version of the Alcohol Use Disorders Identification Test (AUDIT-C) *(262,263)* (see Recommendations 8 and 12). Because depression, anxiety, and other psychological comorbidities often coexist with and can interfere with resolution of pain, clinicians should use validated instruments to assess for these conditions (see Recommendation 8) and ensure that treatment for these conditions is optimized. Clinicians should ask patients about their preferences for continuing opioids considering 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 before initiation of opioid therapy; if patients are taking higher-risk regimens [e.g., dosages of ≥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 taper and reduce opioid dosage or to taper and discontinue opioids when possible (see Recommendation 5). Clinicians should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).

## Assessing Risk and Addressing Potential Harms of Opioid Use

### Recommendation 8

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

#### Implementation Considerations

- Clinicians should ask patients about their drug and alcohol use and use validated tools or consult with behavioral specialists to screen for and assess mental health and substance use disorders.
- When considering initiating long-term opioid therapy, clinicians should ensure that treatment for depression and other mental health conditions is optimized, consulting with behavioral health specialists when needed.
- Clinicians should offer naloxone when prescribing opioids, particularly 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 educate patients on overdose prevention and naloxone use and offer to provide education to members of their households.
- Naloxone coprescribing can be facilitated by clinics or practices with resources to provide naloxone training, by collaborative practice models with pharmacists, or through statewide protocols or 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 https://prescribetoprevent.org . Additional resources are at https://www.samhsa.gov .
- In part because of concerns about cost of naloxone and access for some patients and reports that purchasing of naloxone has in some cases been required to fill opioid prescriptions, including for patients without a way to afford naloxone, this recommendation specifies that naloxone should be offered to patients. To that end, clinicians, health systems, and payers can work to ensure patients can obtain naloxone, a potentially lifesaving treatment.
- Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing when possible to minimize risk for respiratory depression.
- 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 persons already receiving opioids, clinicians should access appropriate expertise if tapering is being considered because of possible risks to the pregnant patient and the fetus if the patient goes into withdrawal (see Recommendation 5).
- For pregnant persons with opioid use disorder, medication for opioid use disorder (buprenorphine or methadone) is the recommended therapy and should be offered as early as possible in pregnancy to prevent harms to both the patient and the fetus (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. Clinicians 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.
- For patients with jobs that involve potentially hazardous tasks and who are receiving opioids or other medications that can negatively affect sleep, cognition, balance, or coordination, clinicians should assess patients' abilities to safely perform the potentially hazardous tasks (e.g., driving, use of heavy equipment, climbing ladders, working at heights or around moving machinery, or working with high-voltage equipment).
- 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 disorders 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 Recommendation 12, Pain Management for Patients with Opioid Use Disorder for additional considerations specific to these patients.)
- 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 (e.g., offering naloxone [see Offering Naloxone to Patients] 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 previous 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 (e.g., 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 for opioid-related harms (*7*). However, on the basis of observational studies (*181,264–273*) 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 over time, such as alcohol use, require more frequent assessment. Clinicians should offer naloxone and reevaluate patients more frequently (see Recommendation 7) when factors are present 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. Experts from OWG had concerns about the cost of purchasing naloxone for patients with limited means and reported that purchasing of naloxone has in some cases been required to fill opioid prescriptions. In part because of these concerns and because in certain settings naloxone is directly provided by a practice or health system to patients, "offering" naloxone (which can be done by offering a prescription or by offering naloxone directly) is recommended rather than specifying "prescribing" naloxone. Clinicians, health systems, and payers should work to ensure patients can obtain 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 was associated with increased risk for life-threatening respiratory/central nervous system depression or overdose (*264*). 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 respiratory depression.

## Pregnant Persons

Pregnant, postpartum, and parenting persons should receive compassionate, evidence-based care for pain or opioid use disorder. ACOG has noted that a cautious approach to prescribing opioids should be balanced with the need to address pain, and pregnancy should not be a reason to avoid treating acute pain (*274*). At the same time, opioid use during pregnancy might be associated with risks to both the pregnant person and the fetus. Certain observational studies have shown an association of opioid use in pregnancy with stillbirth, poor fetal growth, and preterm delivery (*265–268,275*). In some cases, opioid use during pregnancy leads to neonatal abstinence syndrome/neonatal opioid withdrawal syndrome (*269*). ACOG has emphasized that pregnancy should not be a reason to avoid treating acute pain because of concern for opioid misuse or neonatal abstinence syndrome and that neonatal abstinence syndrome is an expected and treatable condition that can follow prenatal exposure to opioid agonists.

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 persons who can become pregnant, clinicians and patients should discuss family planning and potential effects of long-term opioid use on any future pregnancy. For all persons with reproductive potential, discussing future pregnancy intentions and engaging in shared decision-making regarding contraception, if appropriate, is a core component of care. A review of all prescription and nonprescription medications is recommended during prepregnancy and interpregnancy care (*276,277*). Intentional application of a patient-centered reproductive justice framework and use of a shared decision-making model is the recommended approach for providing supportive contraceptive counseling and care to help patients to achieve their reproductive goals (*278*). Counseling should be noncoercive and include a discussion of all contraceptive options (*276–278*). When opioids are needed for treatment of acute pain in pregnant persons, the lowest effective dose (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 persons with chronic pain, ACOG 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, and behavioral approaches), and nonopioid pharmacologic treatments (*274*). Pharmacokinetic and physiologic changes occur during pregnancy, especially in the third trimester, and these changes might require dose adjustments (*274*). For pregnant persons already receiving opioids, clinicians should access appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient and the fetus if the patient goes into withdrawal (see Recommendation 5).

ACOG has noted that early universal screening, brief intervention (e.g., engaging in a short conversation and providing feedback and advice), and referral for treatment of pregnant persons with opioid use disorder improve both maternal and infant outcomes (*274*). For pregnant persons with opioid use disorder, medication for opioid use disorder (buprenorphine or methadone) is the recommended therapy, has been associated with improved maternal outcomes, and should be offered as early as possible in pregnancy to prevent harms to both the patient and the fetus (*274*) (see Recommendation 12). In contrast, criminalization or otherwise punishing (e.g., through threatened loss of child custody) the use of opioids, including for opioid use disorder, discourages pregnant, postpartum, and parenting persons from seeking care; nonpunitive public health approaches to treatment result in better outcomes (*274,279*).

The American Academy of Pediatrics (AAP) has published recommendations for the care of infants with neonatal opioid withdrawal syndrome, including that pregnant persons with opioid use disorder should receive antenatal counseling to provide education on the clinical signs of withdrawal and on postnatal treatment for neonatal opioid withdrawal syndrome (e.g., nonpharmacologic treatment, including breastfeeding, and pharmacotherapy) (*280*). In addition, all infants with long-term opioid exposure should be observed for at least 72 hours (4–7 days if exposed to buprenorphine or ER/LA opioids and 5–7 days if exposed to methadone) to monitor for the development of withdrawal (*280*). Clinicians caring for pregnant persons receiving prescribed or using nonprescribed opioids 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 for the clinician to arrange delivery locally, monitor and evaluate the newborn for neonatal opioid withdrawal syndrome, and transfer the newborn for additional treatment if needed. Previous consensus recommendations have advised that if a codeine-containing medication is selected for postpartum management, clinicians should review duration of therapy and neonatal signs of toxicity with patients and their families (*133*).

## Patients with Renal or Hepatic Insufficiency

A case-control study of risk for 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 these events (*264*). Clinicians should use additional caution and increased monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency because of 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 (*281*) (see Recommendations 3, 4, and 7).

## Patients Aged ≥65 Years

Older adults are a heterogenous group comprising a wide span of ages and functional abilities, ranging from healthy, active older adults to frail older adults. Frail older adults in particular can be at risk for changes in function that might be exacerbated by pain and contribute to deterioration in overall health and independence. Functional assessment is especially important in patients aged ≥65 years to better assess effects of pain on function and independence. Persons aged ≥65 years can be

at risk for inadequate pain treatment (*2,6,17,282*). For certain older adults (e.g., older adults with serious illness that requires advanced management of pain or other distressing symptoms) (*94*), palliative care, which is beyond the scope of this guideline but addressed in other guidelines (*93*), is appropriate.

Pain management for older patients can be challenging because of increased risks of both nonopioid pharmacologic therapies (see Recommendation 2) and opioid therapy in this population. Because of reduced renal function and medication clearance even in the absence of renal disease, patients aged ≥65 years might have increased susceptibility to accumulation of all medications, increased risk for drug-drug interactions, and a smaller therapeutic window between safe dosages and dosages associated with adverse effects. These adverse effects include renal, cardiovascular, and gastrointestinal effects with oral NSAIDs (see Recommendation 2) and respiratory depression and overdose with opioids. 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 (*264*). Some older adults might have a cognitive impairment, such as dementia, that can increase risk for medication errors and make opioid-related confusion riskier. In addition, older adults are more likely than younger adults to experience comorbid medical conditions and are more likely to receive multiple medications, some of which might interact with opioids.

Clinicians should review all current medications, over-the-counter drugs, and natural remedies before prescribing any new drugs. Clinicians should use additional caution and increased monitoring (see Recommendation 7) for patients aged ≥65 years to ensure pain is addressed and minimize risks of opioids prescribed. Clinicians should educate older adults receiving opioids to avoid medication-related behaviors that increase risk, such as saving unused medications. Caregivers can have an important role in management of opioid therapy for older persons with cognitive impairment. Clinicians also should implement interventions to mitigate common risks of opioid therapy among older adults, such as monitoring for cognitive impairment, risk assessment for falls, and exercise and bowel regimens to prevent constipation.

### Patients in Safety Critical Jobs

A safety critical job involves work or an occupational environment where limitations in physical or mental performance, or both, involve dangers to self, coworkers, or the public. According to the American College Occupational Environmental Medicine, for occupations with higher risks (especially public transportation), prescription of an opioid might be incompatible with continued employment in a safety critical job (*270,283*). For patients with safety critical jobs who are receiving opioids or other medications that can negatively affect sleep, cognition, balance, or coordination, clinicians should assess patients' abilities to perform jobs that involve driving, using heavy equipment, climbing ladders, working at heights or around moving machinery, or working with high-voltage equipment.

### Patients with Mental Health Conditions

Psychological distress frequently interferes with improvement of pain and function in patients with chronic pain; therefore, using validated instruments such as the Generalized Anxiety Disorder (GAD)-7 and the Patient Health Questionnaire (PHQ-9 or PHQ-4) to support assessment for anxiety, posttraumatic stress disorder (PTSD), and depression (*284*) might help clinicians improve overall pain treatment outcomes. Patients with mental health conditions including depression might be at higher risk than other patients for opioid use disorder (*181,271*) and drug overdose (*272*). Additional caution and increased monitoring (see Recommendation 7) might lessen the increased risk for overdose among patients with depression (*264,272*). 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 and depression and might decrease overdose risk (*272*). 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 are likely to experience greater risks for opioid use disorder and overdose (*55,202,264*) than persons without these conditions. Despite increased risk for opioid misuse and opioid use disorder when prescribed opioid analgesics (*271,285*), patients with histories of substance use disorders are more likely than other patients to receive long-term opioid treatment for chronic pain (*286*). 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 available risk stratification tools (e.g., Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain [SOAPP] Version 1, SOAPP-R, and Brief Risk Interview) demonstrate limited and variable accuracy for classification of patients as at low or high risk for opioid use disorder or misuse (*7*). 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 use caution when considering or prescribing opioids and should not overestimate the ability of available risk stratification tools to rule out risks of long-term opioid therapy.

Nonprescribed drugs (e.g., heroin, illicitly manufactured fentanyl, cocaine, and methamphetamine) (*287*) and alcohol (*288*) 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 (*289*) and alcohol use. Single screening questions can be used (*290*). 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 (*291*). Validated screening tools, such as the Drug Abuse Screening Test (DAST) (*260*); the Tobacco, Alcohol, Prescription medication, and other Substance use Tool (TAPS) (*261*); and the three-question version of the Alcohol Use Disorders Identification Test (AUDIT-C) (*262,263*), also can 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 prescribing opioid therapy for chronic pain to patients with substance use disorders, they should discuss increased risks for opioid use disorder and overdose with patients; carefully consider whether benefits of opioids outweigh increased risks; and incorporate strategies to mitigate risk into the management plan, such as offering naloxone (see Offering Naloxone to Patients) 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 disorders 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 Recommendation 12, Pain Management for Patients with Opioid Use Disorder for additional considerations.)

### Patients with Previous Overdose

Previous opioid overdose is associated with substantially increased risk for future nonfatal or fatal opioid overdose (*273*). Yet, a cohort study of commercially insured patients found that opioids were dispensed to 91% of patients who had a previous overdose; a substantial percentage experienced a repeated opioid overdose, with a cumulative incidence at 2 years of 17% among patients receiving ≥100 MME/day, 15% among those prescribed 50–100 MME/day, 9% among those prescribed <50 MME/day, and 8% among those prescribed no opioids (*273*).

If patients experience nonfatal opioid overdose, clinicians should evaluate them for opioid use disorder and provide or arrange treatment if needed. Treatment with buprenorphine or methadone for opioid use disorder after overdose is associated with reduced all-cause and opioid-related deaths (*292*). Clinicians should work with patients to reduce opioid dosage and 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 previous 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 offering naloxone (see Offering Naloxone to Patients), involving patient-identified trusted family members, and increasing frequency of monitoring combined with shorter prescription durations (see Recommendation 7).

### Offering Naloxone to Patients

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 (*293*). Naloxone precipitates acute withdrawal among patients physically dependent on opioids. Serious adverse effects (e.g., pulmonary edema, cardiovascular instability, and seizures) have been reported but are rare at doses consistent with labeled use for opioid overdose (*294*). The clinical evidence reviews identified one observational study (*295*) that found provision of naloxone to patients prescribed opioids in primary care clinics was associated with decreased likelihood of opioid-related emergency department visits (*7*).

Clinicians should offer naloxone when prescribing opioids, particularly 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 members of their households. Naloxone coprescribing 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 https://prescribetoprevent.org.

### Recommendation 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 practice is recommended in all jurisdictions where PDMP availability and access policies, as well as clinical practice settings, make it 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. 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 on the basis of assumptions about what they will learn about specific 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, 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 total opioid dosages or combinations (e.g., opioids combined with benzodiazepines) that put the patient at 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 and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of prescription opioids and about 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 disorders [see Recommendations 8 and 12]).
- Clinicians should take actions to improve patient safety:
  - Discuss information from the PDMP with the patient and confirm that the patient is aware of any additional prescriptions. Because clinicians often work as part of teams, prescriptions might appropriately be written by more than one clinician coordinating the patient's care. 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 overlapping prescription opioids from multiple clinicians who are not coordinating the patient's care or patients who are receiving medications that increase risk when combined with opioids (e.g., benzodiazepines) (see Recommendation 11), and offer naloxone (see Recommendation 8).
  - Use particular caution when prescribing opioid pain medication and benzodiazepines concurrently, understanding 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 because of its partial agonist properties at opioid receptors that confer a ceiling effect on respiratory depression. If a patient is found to be receiving total daily dosages of opioids that put them at risk for overdose, discuss safety concerns with the patient, consider in collaboration with the patient whether or not benefits of tapering outweigh risks of tapering (see Recommendation 5), and offer naloxone (see Recommendation 8).
  - Discuss safety concerns with other clinicians who are prescribing controlled substances for the patient. Ideally, clinicians should first discuss concerns with the patient and inform them that they plan to coordinate care with their other clinicians to improve the patient's safety.
  - Screen for substance use and discuss concerns with the patient in a nonjudgmental manner (see Recommendations 8 and 12).
  - When diverting (sharing or selling prescription opioids and not taking them) might be likely, 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 (e.g., 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 and, in selected jurisdictions, by dispensing clinicians. PDMPs do not report nonprescribed opioid use. A clinical evidence review did not find studies evaluating the effectiveness of PDMPs for risk mitigation (*7*). 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 (*296*). PDMP data also can be helpful when patient medication history is not otherwise available (e.g., when patients transition care to a new clinician). A contextual evidence review (*7*) identified a survey of physicians in Maryland (*297*) finding that although barriers to PDMP review were noted (e.g., 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 (*7*). Integration of PDMPs with electronic health records (EHRs) can reduce burden on clinicians compared with having to access a separate system (*298,299*).

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 (*300*), which might adversely affect patient safety and result in untreated or undertreated pain. Many state laws require PDMP use under specific circumstances (*301*). Experts from OWG had concerns 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 proprietary algorithms that are not publicly available to information from patient EHRs and other sources such as court records and criminal and sexual trauma histories; these algorithms might disparately affect women, persons of color, and persons who live in poverty (*302*). Importantly, whereas 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 (*302,303*). 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, to help them communicate with and protect their patient.

Experts raised varying points regarding frequency of PDMP use, with many agreeing that PDMPs should be consulted before 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 before 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 practice is recommended in all jurisdictions where PDMP availability and access policies make it 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. Recommendation category B acknowledges variation in PDMP availability and circumstances (e.g., a clinician might reasonably determine that a patient with severe acute pain in the emergency department during a PDMP system access failure would be adversely affected 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 on the basis of 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 the total amount of MME prescribed and to assess if the total dosage or combinations (e.g., opioids combined with benzodiazepines) put the patient at high risk for overdose. If patients are found to have total 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 Recommendation 9, Implementation Considerations).

## Recommendation 10

**When prescribing opioids for subacute or chronic pain, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances (recommendation category: B; evidence type: 4).**

### Implementation Considerations

- Toxicology testing should not be used in a punitive manner but should be used in the context of other clinical information to inform and improve patient care. Clinicians should not dismiss patients from care on the basis of a toxicology test result. Dismissal 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.
- Before starting opioids and periodically (at least annually) during opioid therapy, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed opioids and 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 in testing and should not apply this recommendation differentially on the basis of assumptions about patients.
- Predicting risk is challenging, and available tools do not allow clinicians to reliably identify patients who are at low risk for substance use or substance use disorders. 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 limitations can be addressed.
- 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 nonprescribed controlled substances not reported by the patient) and ask patients in a nonjudgmental manner about use of prescribed and other drugs and whether there might be unexpected results.
- Limited 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 nonprescribed substances. Toxicology screening for a class of drugs might not detect all drugs in that class. For example, fentanyl testing is not included in widely used toxicology assays that screen for opiates as a class.
- 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 that resulted in the positive test.
- Confirmatory testing should be used when
  - toxicology results will inform decisions with major clinical or nonclinical implications for the patient;
  - a need exists to detect specific opioids or other drugs within a class, such as those that are being prescribed, or those that cannot be identified on standard immunoassays; or
  - a need exists to confirm unexpected screening toxicology test results.
- 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 might want to discuss unexpected results with the local laboratory or toxicologist and should discuss unexpected results with the patient.
- Clinicians should discuss unexpected results with patients in a nonjudgmental manner, avoiding use of potentially stigmatizing language (e.g., avoid describing a specimen as testing "clean" or "dirty").
- Discussion with patients before specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and remove the need for confirmatory testing during that visit. For example, a patient might explain that the test is negative for prescribed opioids because they felt opioids were no longer helping and discontinued them. If unexpected results from toxicology screening are not explained, a confirmatory test on the same sample 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., optimize pain management strategy [see Recommendation 2], carefully weigh benefits and risks of reducing or continuing opioid dosage [see Recommendation 5], reevaluate more frequently [see Recommendation 7], offer naloxone [see Recommendation 8], and offer treatment or refer the patient for treatment with medications for opioid use disorder [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 nonpharmaceutical 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 certain 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 also is available (*304*), although 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 toxicology testing programs of federal executive branch agencies (*305*), effective January 1, 2020. Toxicology testing results can be associated with outcomes and practices that harm patients (e.g., stigmatization and inappropriate termination from care). False positive and false negative presumptive results are not uncommon, a problem that can be compounded because clinicians commonly misinterpret results (*306,307*), leading to inappropriate consequences for patients. Urine toxicology tests do not provide accurate information about how much or what doses of opioids or other drugs a patient took. Testing for fentanyl is not 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 for clinicians in many settings 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 from OWG had concerns that biases and disparities affecting which patients undergo toxicology testing could have disproportionately negative consequences among Black and Hispanic patients. In addition, testing costs would have the greatest consequences for patients with the least ability to pay. Because of these concerns, some experts said that grading the recommendation as category A could potentially reduce bias and disparities. However, others indicated that although universal application could mitigate bias in who is tested, it would not mitigate stigma associated with testing. In addition, experts had concerns about accuracy, clinician interpretation, testing costs, and potential for a delay in care while waiting for test results.

Because of these concerns, 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 on the basis of assumptions about what they will learn about specific patients. Predicting risk is challenging, and available tools do not allow clinicians to reliably identify patients who are at low risk for substance use disorder (*7*). 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; 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.

Before starting opioids and periodically (at least annually) during opioid therapy, clinicians should consider benefits and risks of toxicology testing to assess for prescribed opioids and other prescription and nonprescribed substances that increase risk for overdose when combined with opioids, including nonprescribed 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 nonprescribed 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 for multiple nonprescribed substances. Patients prescribed oxycodone or nonmorphine-based opioids (e.g., buprenorphine or methadone) require specific testing for those agents. The use of confirmatory testing can add costs and should be used when toxicology results will inform decisions with major clinical or nonclinical implications for the patient, a need exists to detect a specific opioid that is prescribed or that cannot be identified on standard immunoassays, or to confirm unexpected toxicology screening results for which there is no other explanation. Clinicians and health systems can 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; however, these agents might 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 (*308*). A review including interpretation of oral fluid sample toxicology test results is also available (*304*). 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 might want to discuss unexpected results with the local laboratory or toxicologist and should discuss unexpected results with the patient. Discussion with patients before specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for confirmatory testing on that visit. For example, a patient might explain that the test is negative for prescribed opioids because they 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], reevaluate more frequently [see Recommendation 7], offer naloxone [see Recommendation 8], and offer or refer patients 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 (*154*).

Clinicians should not dismiss patients from care on the basis of a toxicology test result. Dismissal 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 a substance use disorder.

## Recommendation 11

**Clinicians should use particular 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 in some circumstances 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 particular caution when prescribing opioid pain medication and benzodiazepines concurrently. In addition, clinicians should consider whether benefits outweigh risks for concurrent use of opioids with other central nervous system depressants (e.g., muscle relaxants, nonbenzodiazepine sedative hypnotics, and potentially sedating anticonvulsant medications such as gabapentin and pregabalin).
- Buprenorphine or methadone for opioid use disorder should not be withheld from patients taking benzodiazepines or other medications that depress the central nervous system.
- 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 coprescribed 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 higher-dosage opioids and higher-dosage benzodiazepines in combination, or with use with other substances including alcohol (compared with long-term, stable use of lower-dosage opioids and lower-dosage benzodiazepines without other substances).
- In specific situations, benzodiazepines can be beneficial, and stopping benzodiazepines can be destabilizing.
- Clinicians should taper benzodiazepines gradually before discontinuation because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, rarely, 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., cognitive behavioral therapy), specific antidepressants or other nonbenzodiazepine medications approved for anxiety, or both, should be offered.
- Clinicians should communicate with other 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 (*203,309,310*). The clinical evidence reviews identified three cohort studies that found an association between concurrent use of benzodiazepines and opioids versus opioids alone and increased risk for overdose (*7*). 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 (*311*). The clinical evidence reviews did not find studies evaluating the effectiveness of avoiding coprescribing of benzodiazepines and opioids on risk for overdose (*7*). The clinical evidence reviews identified three observational studies that found an association between concurrent use of gabapentinoids and opioids versus opioids alone and increased risk for overdose, with higher risks at increased gabapentinoid doses (*7*).

Experts from OWG noted that rather than necessarily being a direct cause of overdose, benzodiazepines might serve as a marker of risk for overdose because of underlying conditions, 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. Because of these considerations, multiple experts indicated that recommending extreme caution with concurrent prescription of opioid pain medications 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 in certain circumstances 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-dosage benzodiazepine therapy), clinicians should use particular caution when prescribing opioid pain medication and benzodiazepines concurrently. In addition, because other central nervous system depressants (e.g., muscle relaxants, nonbenzodiazepine sedative hypnotics, and potentially sedating anticonvulsant medications such as gabapentin and pregabalin) (*312*) can potentiate respiratory depression associated with opioids, clinicians should consider whether benefits outweigh risks of concurrent use of these medications. Clinicians should check PDMPs 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 coprescribed 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, as appropriate. In specific situations, benzodiazepines can be beneficial, and stopping benzodiazepines can be destabilizing. As emphasized in an FDA advisory (*313*), buprenorphine or methadone for opioid use disorder should not be withheld from patients taking benzodiazepines or other medications that depress the central nervous system. Whereas 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, decisions about tapering medications (e.g., whether to taper opioids first, taper benzodiazepines first, or consider carefully transitioning from full agonist opioids to buprenorphine before tapering benzodiazepines) should be individualized and reevaluated over time. Considerations include patient priorities, the patient's clinical considerations, the patient's response to therapeutic changes, consultation with other clinicians managing the patient's care, and, consultation with other specialists (e.g., an addiction specialist) if needed. Clinicians should taper benzodiazepines gradually before discontinuation because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, rarely, death (*222,223*). Tapering rates should be individualized. Examples of benzodiazepine tapers and tips for managing benzodiazepine withdrawal are available (*314*). Cognitive behavioral therapy increases tapering success rates and might be particularly helpful for patients struggling with a benzodiazepine taper (*315*). If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., cognitive behavioral therapy), specific antidepressants or other nonbenzodiazepine medications approved for anxiety, or both, 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.

## Recommendation 12

**Clinicians should offer or arrange treatment with evidence-based medications to treat patients with opioid use disorder. Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death (recommendation category: A; evidence type: 1).**

### Implementation Considerations

- Although stigma can reduce the willingness of persons with opioid use disorder to seek treatment, opioid use disorder is a chronic, treatable disease from which persons can recover and continue to lead healthy lives.
- If clinicians suspect opioid use disorder, they should discuss their concern with their patient in a nonjudgmental manner 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 evidence-based treatment with medications for opioid use disorder.
- Clinicians should not dismiss patients from their practice because of opioid use disorder because this can adversely affect patient safety.
- Medication treatment of opioid use disorder has been associated with reduced risk for overdose and overall deaths. Identification of opioid use disorder represents an opportunity for a clinician to initiate potentially life-saving interventions, and the clinician should collaborate with the patient regarding their safety to increase the likelihood of successful treatment.
- For pregnant persons with opioid use disorder, medication for opioid use disorder (buprenorphine or methadone) is the recommended therapy and should be offered as early as possible in pregnancy to prevent harms to both the patient and the fetus.
- Clinicians unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a substance use disorder treatment specialist (e.g., 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 for opioid use disorder.
- Clinicians prescribing opioids should identify treatment resources for opioid use disorder in the community, establish a network of referral options that span the levels of care that patients might need to enable rapid collaboration and referral, when needed, and 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 known as opioid abuse or opioid dependence in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV]) (*316*) is defined in DSM-5 as a problematic pattern of opioid use leading to clinically significant impairment or distress (*317*). Treatment with opioids for pain is associated with increased risk for opioid use disorder, particularly if opioids are prescribed for >90 days (*54*). A systematic review found the rate of opioid addiction among patients with chronic pain averaged 8%–12% in studies published during 2000–2013 (*318*). More recent studies have found prevalence estimates of 23.9%–26.5% for any prescription opioid use disorder and 5.2%–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 (*319,320*).

Opioid use disorder is manifested by at least two of 11 defined criteria occurring within a year (*317*):

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful attempts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
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. a 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) are taken to relieve or avoid withdrawal symptoms.

Criteria 10 and 11 are not considered to be met for those persons taking opioids solely under appropriate medical supervision (*317*). Severity is specified as mild (2–3 criteria), moderate (4–5 criteria), or severe (≥6 criteria) (*317*).

FDA-approved medications indicated for the treatment of opioid use disorder include buprenorphine (a partial agonist opioid), methadone (a full agonist opioid), and naltrexone (an opioid antagonist). Experts from OWG stated that partial agonist opioid, full agonist opioid, and opioid antagonist treatment should not be framed as equal options for opioid use disorder, noting that partial and full agonist opioid treatments have stronger evidence for better outcomes, do not require abstinence, have less challenges with initiation, and are much more widely used than opioid antagonist treatment. Clinical evidence reviews found evidence on the effectiveness of interventions (e.g., medications and behavioral treatments) for opioid use disorder related to prescription opioids to be limited (*7*). However, moderate-quality evidence indicated buprenorphine (a partial agonist opioid) and methadone (a full agonist opioid) to be effective in preventing return to drug use among patients with opioid use disorder involving heroin (*321–323*), although 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 (using DSM-IV criteria) (*316*) and found it to be effective in preventing return to drug use (*324,325*). One study found that among persons with opioid use disorder, previous prescription opioid use predicts stabilization on buprenorphine (*326*). Another trial that performed buprenorphine initiation 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 return to drug use; five of six patients in the maintenance arm completed the trial (*327*). In another trial identified by the clinical evidence reviews, no difference was found between buprenorphine/naloxone and methadone in likelihood of retention in the study and in pain, function, or self-reported side effects (*328*). Buprenorphine and methadone treatment of opioid use disorder has been associated with reduced overdose deaths (*329*) and reduced all-cause deaths (*330*). Naltrexone (an opioid antagonist) also can be used for opioid use disorder, particularly for highly motivated persons (*331,332*). Naltrexone blocks the effects of opioids if they are used. Naltrexone has not been evaluated in persons with concomitant pain and opioid use disorder, and opioid medications for pain generally cannot be used in patients receiving naltrexone. Naltrexone requires

adherence to monthly, long-acting injections. The effectiveness of oral naltrexone can be limited by poor medication adherence (*332*), and oral naltrexone should not be used except under very limited circumstances (*96*) (e.g., for patients who would be able to comply with observed daily dosing to enhance adherence) (*96,317*). Naltrexone also must be started after full withdrawal from opioids, which is a challenge for some patients; however, for patients who have completed or are able to complete withdrawal, naltrexone has comparable effectiveness as buprenorphine in prevention of return to drug use (*333*).

Certain studies suggest that using behavioral therapies in combination with medications for opioid use disorder can reduce opioid misuse and increase retention during treatment (*334,335*). At the same time, a study of treatment for prescription opioid dependence (using DSM-IV criteria) (*316*) found buprenorphine treatment combined with standard medical management (including basic counseling recommending abstinence and self-help group participation) as effective as buprenorphine combined with more intensive opioid dependence counseling (i.e., addiction, recovery, and prevention of return to drug use 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 using drug counseling manuals with demonstrated efficacy); neither standard medical management nor opioid dependence counseling alone, without buprenorphine, was effective in preventing return to drug use (*325*). Recommendations for treatment of opioid use disorder include assessing the patient's psychosocial needs and offering or referring the patient to psychosocial treatment in collaboration with qualified behavioral health care providers based on those needs; however, 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 (*96*). Additional recommendations have been published on goals, components of, and types of effective psychosocial treatment to use in conjunction with pharmacologic treatment of opioid use disorder (*96*).

If clinicians suspect opioid use disorder on the basis of patient concerns or behaviors or on findings in PDMP 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 (*317*). Opioid use disorder can coexist 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 (*96*). 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 evidence-based treatment with medications for opioid use disorder. Patients with opioid use disorder might benefit from counseling and referrals to mutual help groups such as Narcotics Anonymous (*336*), although this should not take the place of treatment with medication. Clinicians also should offer naloxone and training on proper use for overdose reversal to patients with opioid use disorder and to their household members and significant others (*96*) (see Recommendation 8). Clinicians should not dismiss patients from their practice because of opioid use disorder because this can adversely affect patient safety. 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 because of increased risks for return to drug use, overdose, and overdose death (*96*).

For pregnant persons with opioid use disorder, medications for opioid use disorder (buprenorphine or methadone) have been associated with improved maternal outcomes and should be offered as early as possible in pregnancy to prevent harms to both the patient and the fetus (see Recommendation 8) (*133,220*). Previous recommendations have suggested that transmucosal buprenorphine (without naloxone) is preferred during pregnancy to avoid potential prenatal exposure to naloxone, especially if injected, and evidence on the safety of naloxone in pregnant persons remains limited (*96,274*). However, combination buprenorphine/naloxone products are frequently used, a systematic review did not find reports of serious maternal or neonatal outcomes associated with maternal buprenorphine/naloxone use (*337*), and experts have noted that combination products are likely to be safe and effective for pregnant persons when taken as prescribed (*96,274*). ACOG also recommends that if a person is stable on naltrexone before pregnancy, the decision regarding whether to continue naltrexone treatment during pregnancy should involve a careful discussion between the clinician and the patient, weighing the limited safety data on naltrexone with the potential risk for return to drug use with discontinuation of treatment (*274*). For persons receiving buprenorphine or methadone for opioid use disorder and considering breastfeeding, AAP recommends breastfeeding be supported if there has been no return to drug use for ≥90 days and there are no other contraindications, considered if there has been no return to drug use within 30–90 days, and discouraged if there is active substance use or has been a return to drug use within the last 30 days (*280*).

In April 2021, to expand access to buprenorphine, the *Practice Guidelines for the Administration of Buprenorphine for Treating Opioid Use Disorder* (*338*) 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 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 (*339*).

Additional recommendations have been published on initiation, use, and monitoring of buprenorphine treatment for opioid use disorder (*96,336*). 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 poorly absorbed orally; however, if buprenorphine/naloxone is manipulated and injected, naloxone can trigger opioid withdrawal (*340*). In 2018, long-acting injectable formulations of buprenorphine became available (*341*). As a partial agonist, buprenorphine should generally not be initiated until there are objective signs of withdrawal, to avoid precipitating withdrawal. As an alternative for patients not yet in opioid withdrawal, certain studies have described a low-dose initiation approach (sometimes referred to as microdosing) (*342,343*) to avoid precipitating withdrawal when initiating buprenorphine, although evidence regarding this approach is limited. Low-dose buprenorphine initiation is a potential option for patients with opioid use disorder who are taking opioid medications for pain. With this dosing strategy, full agonist opioids can be continued while buprenorphine is initiated, and the patient does not need to experience opioid withdrawal symptoms. For standard (not low-dose) buprenorphine initiation, after objective signs of withdrawal are observed, buprenorphine should be initiated (*96*) and titrated upward under supervision at approximately 2-hour intervals as needed to control withdrawal symptoms. Protocols for initiating buprenorphine by patients at home after an initial encounter with a clinician to establish the diagnosis of opioid use disorder and discuss medication options are in use by more experienced clinicians (*344*).

Importantly, opioid dosage thresholds for caution in the treatment of pain are not applicable to opioid agonist treatment of opioid use disorder (*345*) because recommended dosages of methadone and buprenorphine for opioid use disorder (*96*) differ from those for pain management. No recommended duration limit exists for treatment of opioid use disorder with buprenorphine or methadone, and discontinuation is associated with risks for return to drug use and opioid overdose (*96*). If discontinued, buprenorphine should be tapered very gradually (over several months) (*96*).

Compared with buprenorphine, which can be prescribed by clinicians with a waiver in any setting or dispensed from a SAMHSA-certified opioid treatment program, ongoing methadone treatment for opioid use disorder can only be provided through an opioid treatment program. As short-term exceptions, any clinician may administer (but not prescribe) methadone or buprenorphine to treat acute opioid withdrawal for up to 3 days, while working to refer the patient to opioid use disorder treatment (*346*). Previously, up to a 1-day supply could be administered per day for up to 3 days; in December 2020, Congress directed the Drug Enforcement Administration (DEA) to revise regulations to allow for a 3-day supply of medication to be dispensed at one time (*347*); DEA subsequently advised practitioners how to request exceptions to the 1-day supply limitation pending amendment of 21 CFR 1306.07(b) (*348*). Patients already receiving treatment for opioid use disorder and admitted for other medical reasons may continue to directly receive methadone or buprenorphine treatment in an emergency department or in a hospital throughout inpatient hospitalization (*336,346,349*).

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 (*96*). A minimum of 7–10 days free of opioids is recommended before the first naltrexone dose to avoid precipitation of severe opioid withdrawal (*350*). Extended-release injectable naltrexone is typically administered every 4 weeks by deep intramuscular injection in the gluteal muscle at 380 mg per injection (*96*), alternating buttocks for each subsequent injection (*350*). Certain patients, including those who metabolize naltrexone more rapidly, might benefit from dosing as frequently as every 3 weeks (*96*). Oral naltrexone is no longer recommended and should not be used except under very limited circumstances (*96*). No recommended duration limit exists for treatment of opioid use disorder with naltrexone. If discontinued, naltrexone can be stopped abruptly without precipitating withdrawal symptoms (*96*). Clinicians should warn patients who discontinue naltrexone of the risk for potentially fatal opioid overdose if opioid use is resumed (*96*), because of the loss of tolerance to the previous opioid dosage.

Clinicians are strongly encouraged to provide medication treatment for their patients with opioid use disorder. Those unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a colleague who is able to provide treatment, from a substance use disorder treatment specialist (e.g., 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 clinicians arrange for treatment include SAMHSA's buprenorphine physician locator (https://www.samhsa.gov/medication-assisted-treatment/find-treatment/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, should arrange for patients to follow up with these specialists, and should coordinate continuing care with these specialists. Rapidly identifying appropriate care can be challenging. Treatment need in a community is often not met by capacity to provide buprenorphine or methadone therapy (*351*). 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, technical assistance, and mentors to assist clinicians in assessment for and treatment of substance use disorders, specifically 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, establish a network of referral options that span the levels of care that patients might need to enable rapid collaboration and referral, when needed, and work together to ensure sufficient treatment capacity at the practice level.

### Management of Opioid Misuse That Does Not Meet Criteria for Opioid Use Disorder

Clinicians can have challenges distinguishing between opioid misuse behaviors without opioid use disorder and mild or moderate opioid use disorder (*352*). 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 can 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 also can be considered because of reduced risk for overdose 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 (*96*) (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 also can help with concurrent management of pain (*96*). 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 per day) (*96*) to help manage pain because the duration of effects of buprenorphine is shorter for pain than for suppression of withdrawal (*242*). For severe acute pain (e.g., from trauma or unplanned major surgery) in patients receiving buprenorphine for opioid use disorder, clinicians can consider additional as-needed doses of buprenorphine. In supervised settings, adding a short-acting full agonist opioid to the patient's regular dosage of buprenorphine can be considered without discontinuing the patient's regular buprenorphine dosage; however, if a decision is made to discontinue buprenorphine to allow for more $\mu$-opioid receptor availability, patients should be monitored closely because high doses of a full agonist opioid might be required, potentially leading to oversedation and respiratory depression as buprenorphine's partial agonist effect lessens (*96*). For patients receiving naltrexone for opioid use disorder, short-term use of higher-potency nonopioid analgesics (e.g., NSAIDs) can be considered to manage severe acute pain (*96*). Patients receiving methadone for opioid use disorder who require additional opioids as treatment for severe acute pain management should be monitored carefully, and when feasible, should optimally be treated by a clinician experienced in the treatment of pain in consultation with their opioid treatment program (*96*). The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder (2020 Focused Update) provides additional recommendations (see Part 9) (*96*) 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.

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## Conclusion and Future Directions

CDC indicated the intent to evaluate and reassess the 2016 CDC Opioid Prescribing Guideline as new evidence became available and determine when sufficient new evidence would prompt an update (*56*). CDC funded AHRQ to conduct systematic reviews of the scientific evidence. The following five areas were assessed: 1) noninvasive nonpharmacologic treatments for chronic pain, 2) nonopioid pharmacologic treatments for chronic pain, 3) opioid treatments for chronic pain, 4) treatments for acute pain, and 5) acute treatments for episodic migraine (*7–11*). An update to the 2016 CDC Opioid Prescribing Guideline was warranted on the basis of these reviews.

The new evidence reviews conducted by AHRQ's Evidence-based Practice Centers affirmed the appropriateness of the recommendations in the 2016 CDC Opioid Prescribing Guideline for using opioids to treat chronic pain. The reviews also prompted CDC to modify the recommendations to include acute and subacute pain more explicitly. This updated clinical practice guideline also includes a new topline recommendation for patients who are already receiving ongoing opioid therapy for pain. 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 altogether in accordance with the HHS Tapering Guide (*219,353*).

Four key areas are covered in this clinical practice guideline for prescribing of opioid pain medication for patients aged ≥18 years for pain, excluding pain management related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care. These areas are 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. In addition, five guiding principles were identified to inform implementation across recommendations. These guiding principles focus on 1) the appropriate treatment of pain; 2) flexibility to meet the care needs and clinical circumstances of each patient; 3) a multimodal and multidisciplinary approach to pain management; 4) avoiding misapplication of the clinical practice guideline beyond its intended use; and 5) vigilance in attending to health inequities and ensuring access to 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 regardless of whether opioids are part of a treatment regimen. Clinicians should select nonpharmacologic or pharmacologic treatment modalities, or both, that maximize patient safety and optimize outcomes in pain, function, and quality of life. A multimodal and multidisciplinary approach to pain management that considers the biologic, psychological, and social

characteristics of each person is critical (*6*). The care provided needs to be individualized and person centered (*6*). Clinicians and patients should work together to identify treatment goals, including functional goals, and tailor an approach that considers both the benefits and risks of available options (*6*). Progress should be monitored over time and treatment protocols adjusted accordingly. Health systems and payers can work to ensure multimodal treatment options are available, accessible, and reimbursed for patients. Public and private payers can support a broader array of nonpharmacologic interventions such as exercise, multidisciplinary rehabilitation, mind-body interventions, cognitive behavioral therapy, and certain complementary and integrative medicine therapies (e.g., acupuncture and spinal manipulation) that increasingly are known to be effective (*9*). Reimbursement often is cited as a principle barrier to why these nonpharmacologic treatments are not more widely used (*9*).

An integral part of providing access to and delivery of high-quality health care, including pain treatment, is understanding how the social determinants of health influence the health care provided and the differential outcomes observed (*354*). Social, economic, educational, and neighborhood-level factors might create and exacerbate health inequities that certain persons experience throughout their lives (*354*). 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 (*355*). These inequities affect persons from some racial and ethnic groups, women, persons living in rural areas, persons experiencing homelessness, persons with disabilities, persons with substance use disorders, justice-involved populations, persons with diverse sexual orientation, identity, or gender, and non-U.S. born persons, among others (*356*).

Outcomes such as function and quality of life also are influenced by the health care context (*354*). Differential access to and coverage for high-quality, culturally and linguistically appropriate, health-literate care might influence attitudes toward health care and use of available services (*354*). Prejudice, bias, discrimination, and stereotyping by clinicians, practices, health systems, and payers serve to reinforce these health disparities (*355*). Clinicians, practices, health systems, and payers should attend to health inequities to protect patient safety; guard against unnecessary risks; and ensure access to appropriate, diversified, effective nonpharmacologic and pharmacologic pain management options that are person centered, affordable, accessible, and well coordinated. 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 (*355*).

To avoid unintended consequences for patients, this clinical practice guideline should not be misapplied, or policies derived from it, beyond its intended use (*67*). Examples of misapplication or inappropriate policies include being inflexible on opioid dosage and duration, discontinuing or dismissing patients from a practice, rapidly and noncollaboratively tapering patients who might be stable on a higher dosage, and applying recommendations to populations that are not a focus of the clinical practice guideline (e.g., patients with cancer-related pain, patients with sickle cell disease, or patients during end-of-life care) (*67*).

This clinical practice guideline provides overarching voluntary recommendations on the use of opioids to manage pain. To assist in the uptake and understanding of this new clinical practice guideline, CDC will provide tools and resources for clinicians, health systems, patients, and others on the use of opioid and nonopioid pain treatments. The uptake and widespread use of the 2016 CDC Opioid Prescribing Guideline hinged on its successful dissemination, and CDC supported its translation and integration in clinical practice. CDC produced a checklist and mobile app so clinicians could more readily apply guideline recommendations; developed fact sheets, posters, and public service announcements to make the guideline more accessible and understandable to clinicians and patients; and developed a 14-module interactive, web-based training with self-paced learning, case-based content, knowledge checks, and integrated resources for clinicians (*57*). Updated and new resources and tools will align with this new clinical practice guideline and will support health equity.

CDC will work with public and private payers by sharing evidence that can be used to inform decisions about coverage for nonpharmacologic treatments, access to nonopioid pain medication, support for patient counseling and coordination of care, access to evidence-based treatments of opioid use disorder, and 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 facilitate and encourage evidence-based treatments as default treatments for pain (*357,358*).

This clinical practice guideline updates and expands the recommendations in the 2016 CDC Opioid Prescribing Guideline using the best available evidence as interpreted and informed by expert opinion and attending to the values and preferences expressed by patients, caregivers, and clinicians. Although the strength of the evidence is sometimes low quality and research gaps remain (Box 5), clinical scientific evidence continues to advance and supports the recommendations in this clinical practice guideline (*6–11,359*).

The principal aim of this clinical practice guideline is to ensure persons have equitable access to safe and effective pain management that improves their function and quality of life while illuminating and reducing risks associated with prescription opioids. CDC will evaluate this clinical practice guideline to identify the effects of the recommendations on clinician and patient outcomes and on health disparities, including intended and unintended consequences. Communication between clinicians and patients about the benefits and risks 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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## Conflicts of Interest and Disclosures of Relationship

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## BOX 1. Executive summary of the CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022

This clinical practice guideline updates and expands the *CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016* (MMWR Recomm Rep 2016;65[No. RR-1]:1–49]) and provides evidence-based recommendations for primary care and other clinicians (including physicians, nurse practitioners and other advanced practice registered nurses, physician assistants, and oral health practitioners) providing pain care, including those prescribing opioids, for outpatients aged ≥18 years with acute (duration of <1 month) pain, subacute (duration of 1–3 months) pain, or chronic (duration of >3 months) pain. Recommendations on use of opioids for acute pain and on tapering opioids for patients already receiving opioid therapy have been substantially expanded in this update. These recommendations do not apply to patients experiencing pain associated with the following conditions or settings: pain management related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care. Applicable outpatient settings include clinician offices, clinics, and urgent care centers. The recommendations do not apply to providing care to patients who are hospitalized or in an emergency department or other observational setting from which they might be admitted to inpatient care. These recommendations do apply to prescribing for pain management when patients are discharged from hospitals, emergency departments, or other facilities.

This clinical practice guideline addresses the following 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
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; values and preferences of patients, caregivers, and clinicians; and resource allocation (e.g., costs to patients or health systems, including clinician time). CDC obtained input on this clinical practice guideline through individual conversations with patients, caregivers, and clinicians and public comment opportunities available via *Federal Register* notices. CDC also sought input from the Board of Scientific Counselors of the National Center for Injury Prevention and Control (BSC/NCIPC) (a federally chartered advisory committee), federal partners, and peer reviewers with scientific and clinical expertise.

The clinical evidence reviews found that a number of nonpharmacologic treatments and a number of nonopioid medications are associated with improvements in pain, function, or both, that appear comparable to improvements associated with opioid use. Multiple noninvasive nonpharmacologic interventions (e.g., exercise and psychological therapies) are associated with improvements in pain, function, or both, that are sustained after treatment and are not associated with serious harms. Nonopioid drugs, including serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants, pregabalin and gabapentin, and nonsteroidal anti-inflammatory drugs (NSAIDs), are associated with small to moderate improvements in chronic pain and function for certain chronic pain conditions. Nonopioid 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 and with small improvements in short-term (1 to <6 months) pain and function compared with placebo; evidence was found of attenuated pain reduction over time with opioids (between 3 and 6 months versus between 1 and 3 months). Opioid therapy is associated with increased risk for serious harms (including opioid use disorder and overdose) that appears to increase with increase in opioid dosage, without a clear threshold below which there is no risk. No validated, reliable way exists to predict which patients will suffer serious harm from opioid therapy. Evidence was sparse for long-term improvement of pain or function for any treatment for chronic pain. Some evidence indicated that beneficial effects of some nonpharmacologic therapies persist for up to 12 months after the end of a course of a treatment. Among 154 trials of nonopioid medications rated as good or fair quality, eight were long term (≥1 year). A single trial evaluated outcomes at 1 year for opioid medications (compared with nonopioid medications).

CDC invited input on the draft clinical practice guideline and received approximately 5,500 public comments. Many of these comments were related to experiences with pain or with the aftermath of a family member's, friend's, or significant person's overdose; barriers to and access to pain care and evidence-based treatment; concerns about the level of specificity of recommendations; and overall communication and implementation of the clinical practice guideline. Some respondents expressed concerns that insufficient specificity of recommendations might leave clinicians without sufficient practical advice or context, whereas others were concerned that inclusion of more-specific recommendations or information in the guideline could facilitate misapplication through adaption of the clinical practice guideline or components of the guideline into rigid policies and laws. CDC incorporated insights from public comments into the clinical practice guideline, including special considerations for each recommendation. To help prevent misapplication of recommendations as inflexible rules and enable clinicians to account for individualized, person-centered clinical considerations, specific prescription dosages and durations are generally not included in the summary recommendation statements, which highlight general principles. Greater specificity is provided in implementation considerations and supporting rationales, which can offer more flexibility to help clinicians weigh benefits and risks of different therapeutic courses for specific patients.

Recommendation statements emphasize that opioids should be used only when benefits for pain and function are expected to outweigh risks. Before initiating opioid therapy for patients with pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy. Before starting ongoing opioid therapy for patients with subacute or chronic pain, clinicians should 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 and reviewing potential interactions with any other prescribed medications or substances used. Clinicians should offer or arrange treatment with evidence-based medications to treat patients with opioid use disorder.

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. 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). Quality and equitable care across sociodemographic groups requires attention to mitigation of potential barriers to care, such as 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 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 health care professionals; health systems; pharmacies; third-party payers; or state, local, or federal organizations or entities. This clinical practice guideline is intended to improve communication between clinicians and patients about the benefits and risks of pain treatment, including opioid therapy for pain; improve the safety and effectiveness 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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### BOX 2. Intended use of CDC's Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022

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 with
  - acute pain (duration of <1 month),
  - subacute pain (duration of 1–3 months), or
  - chronic pain (duration of >3 months); and
- intended to be flexible to enable person-centered decision-making, taking into account a patient'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 or patient populations by health care professionals, health systems, pharmacies, third-party payers, or governmental jurisdictions or to lead to the rapid tapering or abrupt discontinuation of opioids for patients;
- a law, regulation, or policy that dictates clinical practice or as a substitute for Food and Drug Administration–approved labeling;
- applicable to
  - management of pain related to sickle cell disease,
  - management of cancer-related pain, or
  - palliative care or end-of-life care; or
- focused on opioids prescribed for opioid use disorder.

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### BOX 3. Recommendations for prescribing opioids for outpatients with pain, excluding pain management related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care; recommendation categories; and evidence types — CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022

#### Determining Whether or Not to Initiate Opioids for Pain (Recommendations 1 and 2)

1. Nonopioid therapies are at least as effective as opioids for many common types of acute pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient. Before prescribing opioid therapy for acute pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy (recommendation category: B; evidence type: 3).
2. Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and 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 realistic benefits and known risks 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).

#### Selecting Opioids and Determining Opioid Dosages (Recommendations 3, 4, and 5)

3. When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids (recommendation category: A; evidence type: 4).
4. When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage. 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 opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage. If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy. If benefits do not outweigh risks 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 circumstances of the patient, 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 rapidly reduce opioid dosages from higher dosages (recommendation category: B; evidence type: 4).

#### Deciding Duration of Initial Opioid Prescription and Conducting Follow-Up (Recommendations 6 and 7)

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 1–4 weeks of starting opioid therapy for subacute or chronic pain or of dosage escalation. Clinicians should regularly reevaluate benefits and risks of continued opioid therapy with patients (recommendation category: A; evidence type: 4).

#### Assessing Risk and Addressing Potential Harms of Opioid Use (Recommendations 8, 9, 10, 11, and 12)

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss risk with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone (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 the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances (recommendation category: B; evidence type: 4).
11. Clinicians should use particular 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 evidence-based medications to treat patients with opioid use disorder. Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death (recommendation category: A; evidence type: 1).

**Recommendation categories** (on basis of 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 types** (on basis of study design and 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.

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### BOX 4. Guiding principles for implementation of the CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022 recommendations

1. Acute, subacute, and chronic pain needs to be appropriately assessed and 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 is 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 clinical practice guideline beyond its intended use or implementing policies purportedly derived from it that might lead to unintended and potentially harmful consequences for patients.
5. Clinicians, practices, health systems, and payers should vigilantly attend to health inequities; provide culturally and linguistically appropriate communication, 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.

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### TABLE. Morphine milligram equivalent doses for commonly prescribed opioids for pain management

| Opioid | Conversion factor* |
|---|---|
| Codeine | 0.15 |
| Fentanyl transdermal (in mcg/hr) | 2.4 |
| Hydrocodone | 1.0 |
| Hydromorphone | 5.0 |
| Methadone | 4.7 |
| Morphine | 1.0 |
| Oxycodone | 1.5 |
| Oxymorphone | 3.0 |
| Tapentadol† | 0.4 |
| Tramadol§ | 0.2 |

**Sources:** Adapted from Von Korff M, Saunders K, Ray GT, et al. Clin J Pain 2008;24:521–7 and Nielsen S, Degenhardt L, Hoban B, Gisev N. Pharmacoepidemiol Drug Saf 2016;25:733–7.
**Abbreviations:** mcg/hr = microgram per hour; mg = milligram; MME = morphine milligram equivalent.

* 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 10 mg and taken twice a day would contain a total of 20 mg 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 because of 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 because 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 because of their partial $\mu$-receptor agonist activity and resultant ceiling effects compared with 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; however, it is unknown whether 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; however, it is unknown whether 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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### BOX 5. Areas for additional research to build the evidence base for optimal pain management

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- Efficacy of screening tools to assess risk for opioid misuse and developing an opioid use disorder.
- Effective management of patients on high-dosage 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 for chronic pain, including effects of treatment combinations, dosage variation, and comorbidities.
- Comparative effectiveness and comparative risks of partial agonist opioids (e.g., buprenorphine) versus full agonist opioids for pain.
- Comparative effectiveness and risks of interventional procedures as part of a comprehensive pain management plan.
- Effects of therapies on nonpain outcomes.
- Treatment outcomes for specific pain conditions and how benefits and risks of therapies vary among subpopulations.
- Adapting evidence-based opioid prescribing and pain management strategies to meet the needs of special populations, including persons from some racial and ethnic groups, older adults, and persons living in rural communities.
- Effectiveness of clinician and health system strategies to promote equitable access to high-quality pain management.
- Improved diagnostics in measuring pain.
- Enhanced clinician and patient education about pain and the use of opioids, and 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.
- Effects of stigma as a barrier for treating pain and receiving treatment for an opioid use disorder, and effective ways to counter the effects of stigma on access to treatment for pain and opioid use disorder.

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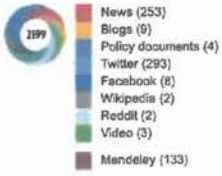


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SAMHSA

Substance Abuse and Mental Health Services Administration

# Removal of DATA Waiver (X-Waiver) Requirement

Section 1262 of the Consolidated Appropriations Act, 2023 (also known as Omnibus bill), removes the federal requirement for practitioners to submit a Notice of Intent (have a waiver) to prescribe medications, like buprenorphine, for the treatment of opioid use disorder (OUD). With this provision, and effective immediately, SAMHSA will no longer be accepting NOIs (waiver applications).

All practitioners who have a current DEA registration that includes Schedule III authority, may now prescribe buprenorphine for Opioid Use Disorder in their practice if permitted by applicable state law and SAMHSA encourages them to do so. SAMHSA and DEA are actively working on implementation of a separate provision of the Omnibus related to training requirements for DEA registration that becomes effective in June 2023. Please continue to check this webpage for further updates and guidance.

**275 Annual Report**

275 Annual Reports are no longer required or being accepted.

Last Updated: 01/25/2023

**Source:** https://www.samhsa.gov/medications-substance-use-disorders/removal-data-waiver-requirement

An official website of the United States government
Here's how you know

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# Drug Enforcement Administration

Headquarters

@DEAHQ <https://twitter.com/deahq>

**February 24, 2023**

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**For Immediate Release**

# DEA Announces Proposed Rules for Permanent Telemedicine Flexibilities

## DEA extends many telemedicine flexibilities adopted during the COVID-19 PHE with appropriate safeguards

**WASHINGTON** - Today, the Drug Enforcement Administration announced proposed permanent rules for the prescribing of controlled medications via telemedicine, expanding patient access to critical therapies beyond the scheduled end of the COVID-19 public health emergency <https://www.deadiversion.usdoj.gov/coronavirus.html>. The public will be able to comment for 30 days on the proposed rules.

The proposed rules – developed with the U.S. Department of Health and Human Services and in close coordination with the U.S. Department of Veterans Affairs – propose to extend many of the flexibilities adopted during the public health emergency with appropriate safeguards.

The proposed rules **do not affect**:

- Telemedicine consultations that do not involve the prescribing of controlled medications.
- Telemedicine consultations by a medical practitioner that has previously conducted an in-person medical examination of a patient.

The proposed rules also would not affect:

- Telemedicine consultations and prescriptions by a medical practitioner to whom a patient has been referred, as long as the referring medical practitioner has previously conducted an in-person medical examination of the patient.

The proposed rules would provide safeguards for a narrow subset of telemedicine consultations — those telemedicine consultations by a medical practitioner that has: never conducted an in-person evaluation of a patient; AND that result in the prescribing of a controlled medication. For these types of consultations, the proposed telemedicine rules would allow medical practitioners to prescribe:

- a 30-day supply of Schedule III-V non-narcotic controlled medications;
- a 30-day supply of buprenorphine for the treatment of opioid use disorder

without an in-person evaluation or referral from a medical practitioner that has conducted an in-person evaluation, as long as the prescription is otherwise consistent with any applicable Federal and State laws. The proposed rules are explained in further detail for patients and medical practitioners on DEA.gov.

"DEA is committed to ensuring that all Americans can access needed medications," said DEA Administrator Anne Milgram. "The permanent expansion of telemedicine flexibilities would continue greater access to care for patients across the country, while ensuring the safety of patients. DEA is committed to the expansion of telemedicine with guardrails that prevent the online overprescribing of controlled medications that can cause harm."

"Improved access to mental health and substance use disorder services through expanded telemedicine flexibilities will save lives," said HHS Secretary Xavier Becerra. "We still have millions of Americans, particularly those living in rural communities, who face difficulties accessing a doctor or health care provider in-person. At HHS, we are committed to working with our federal partners and stakeholders to advance proven technologies and lifesaving care for the benefit of all Americans."

The proposed telemedicine rules also further DEA's goal of expanding access to medication for opioid use disorder to anyone in the country who needs it. "Medication for opioid use disorder helps those who are fighting to overcome substance use disorder by helping people achieve and sustain recovery, and also prevent drug poisonings," said DEA Administrator Milgram. "The telemedicine regulations would continue to expand access to buprenorphine for patients with opioid use disorder."

The full text of the proposals may be found here <https://www.federalregister.gov/d/2023-04217> and here <https://www.federalregister.gov/d/2023-04248>. The public has 30 days to review and comment on the proposals, which DEA will then consider before drafting final regulations. DEA is appreciative of the public's feedback.

For more information on DEA's continued efforts to expand access to medications used in treatment for those suffering from opioid use disorder, visit: DEA's Commitment to Expanding Access to Medication-Assisted Treatment. <https://www.dea.gov/press-releases/2022/03/23/deas-commitment-expanding-access-medication-assisted-treatment>

Additional resources for patients can be found here:

- Is My Prescription a Controlled Medication? Controlled-Non Controlled List (dea.gov) <https://www.dea.gov/sites/default/files/2023-02/prescription%20controlled.pdf>
- Can My Medication be Prescribed through Telemedicine? Controlled Substance Guidance (dea.gov) <https://www.dea.gov/sites/default/files/2023-02/controlled%20substance%20guidance.pdf>

Additional resources for practitioners can be found here:

- Proposed Rules Summary Telemedicine Rules Summary.pdf (dea.gov) <https://www.dea.gov/sites/default/files/2023-02/telemedicine%20rules%20summary.pdf>
- Proposed Rules Highlights for Medical Practitioners Telehealth Practitioner Narrative.pdf (dea.gov) <https://www.dea.gov/sites/default/files/2023-03/telehealth_practitioner_narrative_312023.pdf>

###

The Drug Enforcement Administration encourages that all comments be submitted through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the Web page or to attach a file for lengthier comments. Please go to http://www.regulations.gov/ <http://www.regulations.gov/> and follow the online instructions at that site for submitting comments.

## Proposed Telemedicine Rules Summary

| Relationship between prescribing medical practitioner and patient | Prescribing a non-controlled medication | Prescribing Schedule III, IV, or V non-narcotic controlled medications | Prescribing buprenorphine as medication for opioid use disorder | Prescribing Schedule II and/or narcotic controlled medications |
|---|---|---|---|---|
| **Prior in-person medical evaluation by prescribing medical practitioner** | Permitted | Permitted | Permitted | Permitted |
| **Referral under the proposed rules from medical practitioner who conducted prior in-person medical evaluation** | Permitted | Permitted | Permitted | Permitted |
| **Telehealth visit without:**<br>• **Prior in-person medical evaluation by prescribing medical practitioner; or**<br>• **Referral from a medical practitioner who conducted prior in-person medical evaluation** | Permitted | • Up to 30-day initial prescription<br>• In-person visit required for additional prescription | • Up to 30-day initial prescription<br>• In-person visit required for additional prescription | Not permitted |

- *Telemedicine prescriptions must be otherwise consistent with applicable state and federal laws.*

## Morton, Colanthia D. (DHP)

**From:** Harp, William L. (DHP) <William.Harp@DHP.VIRGINIA.GOV>
**Sent:** Monday, March 13, 2023 4:00 PM
**To:** Morton, Colanthia D. (DHP)
**Subject:** Fw: Co-prescribing rule
**Attachments:** Commonwealth_of_Virginia_Board_of_Medicine07272022.pdf

Petition for Rulemaking

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**From:** Todd Lacksonen <tlacksonen@opiant.com>
**Sent:** Wednesday, July 27, 2022 6:34 AM
**To:** Harp, William L. (DHP) <William.Harp@DHP.VIRGINIA.GOV>
**Subject:** RE: Co-prescribing rule

William,

Good morning, how are you?

Please find attached our proposed rule change submission.

Please let me know if you have any question or need anything further.

Without being overly assertive and this being my first rule change submission are you able to share with me at a high-level the timeline and process? And if the Board needs further documentation or discussion, please let me know.

Kindest regards,

Todd Lacksonen

**From:** Harp, William <william.harp@dhp.virginia.gov>
**Sent:** Tuesday, July 19, 2022 11:38 AM
**To:** Todd Lacksonen <tlacksonen@opiant.com>
**Cc:** erin.barrett@dhp.virginia.gov
**Subject:** Re: Co-prescribing rule

Dear Mr. Lacksonen:

Thank you for your message.

The Virginia Board of Medicine is unable to offer advice to you and Opiant in regards to a change in the Board's regulations. Therefore, a meeting is not necessary.

That said, I am including the link to the Board of Medicine's Petition for Rule-Making and invite you to follow the process to request the change you seek. https://www.dhp.virginia.gov/media/dhpweb/docs/med/leg/Medicine_Petition.pdf

I hope this is helpful to you.

With kindest regards,

Willam L. Harp, MD
Executive Director
Virginia Board of Medicine

On Tue, Jul 19, 2022 at 10:37 AM Todd Lacksonen <tlacksonen@opiant.com> wrote:

William and Erin,

Good morning, I hope this message finds you both very well.

I am writing to introduce myself and my company Opiant as well as to discuss the status of Virginia's rule requiring the co prescription of naloxone with an opioid prescription under certain conditions. We would like to arrange an appointment to seek your guidance regarding a prospective amendment to the current rule to accommodate any next generation overdose reversal drugs.

http://www.dhp.virginia.gov/media/dhpweb/docs/med/leg/Medicine_Opioid_Regs_06092021.pdf

The co-prescribing language:

3. Naloxone shall be prescribed for any patient when risk factors of prior overdose, substance misuse, doses in excess of 120 MME/day, or concomitant benzodiazepine is present.

It is our understanding after conversations with our contacts at the Medical Society of Virginia and the Virginia Academy of Family Physicians that the Board of Medicine has the authority to promulgate relevant rule changes. It is not clear if my company would request such consideration , or if the Board can initiate without a request from a third party. We would want to substitute any reference to naloxone with molecule neutral language, such as 'any FDA approved reversal drug.' We are in the process of seeking similar substitutions in applicable state laws across the US.

I would welcome the opportunity to discuss and would be happy to meet with you both in the Commonwealth.

Kindest regards,

Todd Lacksonen

opiant

**Todd Lacksonen** / Director of Government Affairs
tlacksonen@opiant.com / O: (310) 598-5410 M: (614) 582-3003

**Opiant Pharmaceuticals**
233 Wilshire Blvd, Suite 280, Santa Monica, CA 90401
www.opiant.com

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# COMMONWEALTH OF VIRGINIA
# Board of Medicine

9960 Mayland Drive, Suite 300
Richmond, Virginia 23233-1463

(804) 367-4600 (Tel)
(804) 527-4426 (Fax)
Coco.Morton@dhp.virginia.gov


## Petition for Rule-making

*The Code of Virginia (§ 2.2-4007) and the Public Participation Guidelines of this board require a person who wishes to petition the board to develop a new regulation or amend an existing regulation to provide certain information. Within 14 days of receiving a valid petition, the board will notify the petitioner and send a notice to the Register of Regulations identifying the petitioner, the nature of the request and the plan for responding to the petition. Following publication of the petition in the Register, a 21-day comment period will begin to allow written comment on the petition. Within 90 days after the comment period, the board will issue a written decision on the petition. If the board has not met within that 90-day period, the decision will be issued no later than 14 days after it next meets.*

**Please provide the information requested below. (Print or Type)**

| | | |
|---|---|---|
| **Petitioner's full name (Last, First, Middle initial, Suffix,)**<br>Todd Lacksonen/Opiant Pharmaceuticals | | |
| **Street Address**<br>8732 Tayport Drive | **Area Code and Telephone Number**<br>614 582 3003 | |
| **City**<br>Dublin | **State**<br>Ohio | **Zip Code**<br>43017 |
| **Email Address (optional)**<br>tlacksonen@opiant.com | **Fax (optional)** | |

**Respond to the following questions:**

1. What regulation are you petitioning the board to amend? Please state the title of the regulation and the section/sections you want the board to consider amending.

   18VAC85-21-40. Treatment of acute pain with opioids.
   3. Naloxone shall be prescribed for any patient when risk factors of prior overdose, substance misuse, doses in excess of 120 MME/day, or concomitant benzodiazepine is present.

2. Please summarize the substance of the change you are requesting and state the rationale or purpose for the new or amended rule.

   We suggest the substitution of "naloxone" with "all FDA-approved opioid-reversal agents" to assure optimal clinical choices for physicians treating patients who by definition (and policy intent) are at a greater risk of overdose.

3. State the legal authority of the board to take the action requested. In general, the legal authority for the adoption of regulations by the board is found in § 54.1-2400 of the Code of Virginia. If there is <u>other</u> legal authority for promulgation of a regulation, please provide that Code reference.

   § 54.1-2400. General powers and duties of health regulatory boards section 6: To promulgate regulations in accordance with the APA Act (§ 2.2-4000 et seq.) that are reasonable and necessary to administer effectively the regulatory process

**Signature:** DocuSigned by: Todd Lacksonen 64CEC94C1D0A40D...

**Date:** July 27, 2022

## Morton, Colanthia D. (DHP)

**From:** Harp, William L. (DHP) <William.Harp@DHP.VIRGINIA.GOV>
**Sent:** Monday, March 13, 2023 3:57 PM
**To:** Morton, Colanthia D. (DHP)
**Subject:** Fw: naloxone co-prescribing rule comments
**Attachments:** VA BOM Testimony - FINAL (002).docx

RAP Packet

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**From:** Todd Lacksonen <tlacksonen@opiant.com>
**Sent:** Monday, September 19, 2022 2:41 PM
**To:** Board of Medicine <medbd@DHP.VIRGINIA.GOV>; Harp, William L. (DHP) <William.Harp@DHP.VIRGINIA.GOV>
**Subject:** naloxone co-prescribing rule comments

Good afternoon,

I am submitting a copy of the comments I submitted today on behalf of Opiant Pharmaceuticals concerning a proposed change to the naloxone co-prescribing rule.

Kindest regards,

Todd Lacksonen

opiant

**Todd Lacksonen** / Director of Government Affairs
tlacksonen@opiant.com / O: (310) 598-5410 M: (614) 582-3003

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September 14, 2022
L. Blanton Marchese, MD
President, Virginia Board of Medicine
9960 Maryland Drive, Suite 300
Henrico, Virginia 23233
RE: Comments in Support of Petition 372

Dear President Marchese and members of the Board,

Currently, I serve as Chief Scientific Officer at Opiant Pharmaceuticals. While serving as the Director of the National Institute on Drug Abuse's Division of Therapeutics and Medical Consequences, I led the team developing the 4mg naloxone nasal spray that is now the 'gold standard' for treating opioid overdose.

On behalf of my organization and the dedicated researchers who contributed to the development of the 4mg naloxone nasal spray, we wish to offer our support for the proposed amendment to the Commonwealth of Virginia's Board of Medicine co-prescribing rule (18VAC85-21-70) that would expand the current rules governing co-prescribing of naloxone under certain conditions to also include anticipated future FDA-approved overdose treatments that are different from naloxone. The proposed agent agnostic language is intended to ensure that physicians have all therapeutic options available when contemplating the most suitable opioid overdose reversal agent.

High-potency synthetic opioids like fentanyl are now responsible for almost 90% of opioid overdose deaths in the United States, and innovative reversal agents are being developed which may be better suited to reverse an overdose caused by synthetic opioids. As these agents become available, they will offer practitioners additional choices to offer to their patients, but the existing rule currently limits those options. We ask that the language be expanded to the drug class instead of being limited to naloxone. Updated language suggestions include:

- *"FDA-approved opioid reversal agent,"* consistent with recent Substance Abuse and Mental Health Services Administration (SAMHSA) grant notices of funding opportunities.
- *"Naloxone or other opioid antagonist,"* which is consistent with other Virginia code sections.

The following are references of the Virginia statutes that reference opioid antagonists:

- **§ 18.2-251.03. Arrest and prosecution when experiencing or reporting overdoses.**
- **§ 54.1-3408. Professional use by practitioners.**
- **§ 32.1-45.4. Comprehensive harm reduction programs.**
- **§ 32.1-127. Regulations.**

This language update in the Virginia Board of Medicine Rules is necessary because there are multiple overdose reversal agents products in development that utilize active ingredients other than naloxone. An example of one of these innovative products is Opiant's nalmefene nasal spray, which we are in the process of filing our NDA. This rule will ensure that physicians in Virginia can exercise their clinical judgement and select any reversal agent they deem appropriate.

When updated, the co-prescribing provisions of the rule will allow all opioid-reversal agents to be considered and ensures that Virginians are not left without critical tools to combat opioid overdose.

**Updating Molecule-Specific Language:**

In 2017, the National Institute of Health asked to "work with private partners to develop stronger, longer-acting formulations of antagonists, including naloxone, to counteract the very-high-potency synthetic opioids that are now claiming thousands of lives each year.[1]" Opiant and other innovators in overdose reversal want to ensure that Virginia residents will be able to access any FDA-approved reversal agent.

**Co-Prescription**

Co-prescription of opioid overdose reversal agents is one of the most effective strategies available for preventing overdose death. According to research published in the *Annals of Internal Medicine*[2], patients who received an opioid overdose antagonist with their long-term opioid prescription had 47% fewer opioid-related emergency room visits after six months and 63% fewer after one year, compared to patients who did not receive it an opioid antagonist. Co-prescription rules exist in 15 states and have been seen as an effective way to identify at-risk individuals and ensure they receive a consultation on an overdose reversal agent.

This administrative rule change will help ensure that Virginians have access to all opioid reversal agents. We would be happy to answer any questions or address concerns any members of the Board may have. Thank you for your consideration.

Sincerely yours,

Phil Skolnick, PhD., DSc. (hon.)
Chief Scientific Officer

[1] (Nora D. Volkow, 2017)
[2] (Phillip O. Coffin, Emily Behar, Christopher Rowe, Glenn-Milo Santos, & Diana Coffa, 2016)

frontiers in Pain Research

REVIEW
published: 17 August 2021
doi: 10.3389/fpain.2021.721357

# Opioids and Chronic Pain: An Analytic Review of the Clinical Evidence

*Stephen E. Nadeau*[1]*, *Jeffrey K. Wu*[2] *and Richard A. Lawhern*[3]

[1] *Research Service and the Brain Rehabilitation Research Center, Malcom Randall VA Medical Center and the Department of Neurology, University of Florida College of Medicine, Gainesville, FL, United States,* [2] *Cornell University, Ithaca, NY, United States,* [3] *Independent Researcher and Patient Advocate, Fort Mill, SC, United States*

We conducted an analytic review of the clinical scientific literature bearing on the use of opioids for treatment of chronic non-cancer pain in the United States. There is substantial, albeit not definitive, scientific evidence of the effectiveness of opioids in treating pain and of high variability in opioid dose requirements and side effects. The estimated risk of death from opioid treatment involving doses above 100 MMED is ~0.25%/year. Multiple large studies refute the concept that short-term use of opioids to treat acute pain predisposes to development of opioid use disorder. The prevalence of opioid use disorder associated with prescription opioids is likely <3%. Morbidity, mortality, and financial costs of inadequate treatment of the 18 million Americans with moderate to severe chronic pain are high. Because of the absence of comparative effectiveness studies, there are no scientific grounds for considering alternative non-pharmacologic treatments as an adequate substitute for opioid therapy but these treatments might serve to augment opioid therapy, thereby reducing dosage. There are reasons to question the ostensible risks of co-prescription of opioids and benzodiazepines. As the causes of the opioid crisis have come into focus, it has become clear that the crisis resides predominantly in the streets and that efforts to curtail it by constraining opioid treatment in the clinic are unlikely to succeed.

**Keywords: opioids, opioid efficacy, opioid dosage, opioid mortality, opioid use disorder, opioid crisis, opioid crisis causes**

OPEN ACCESS

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## INTRODUCTION

The opioid crisis, already of staggering proportions, continues to grow despite many years of effort within the field of medicine, the issuance of treatment guidelines, and substantial legislative action across the nation. At the same time, we find ourselves at an impasse. On the one hand, we have the scientific knowledge to substantially address the crisis. On the other hand, the combination of efforts by physicians concerned with rising opioid mortality, the issuance of a national guideline by the Centers for Disease Control and Prevention (CDC) (1), and legislative action has not had a measurable impact on the crisis. Worse, it has spawned a second crisis (2), this one involving Americans who have relied for years on opioid treatment to manage chronic pain and enable them to contribute to society and enjoy some quality of life. Epidemiologic studies suggest that 22% of U.S. adults (55 million) experience chronic pain and 7% (18 million) moderate to severe pain (3). These patients now face disability, inordinate suffering, and excess mortality. Given these two crises,

it seems timely to re-assess the scientific evidence and examine its implications for medical practice, public policy, and further research.

Our particular focus will be on issues relevant to clinical decision making by the practitioner; clarification of the research questions that need to be addressed; and clinical trial experimental designs that may be able to address questions in this field that have stymied conventional designs. Our review involved particularly careful analysis of study methodology and data with an attempt to incorporate the full dimensionality of chronic pain and its treatment in each assessment. Some perspectives on the opioid crisis have been substantially influenced by misperceptions [reviewed by Oliver and Carlson (4)].

This analysis is based almost entirely on American literature. There may be much for other countries to learn from the American experience. However, the particular characteristics of the opioid crisis in America reflect cultural influences, the extraordinary heterogeneity of American society, the existence of large pockets of poverty, the absence of comprehensive health care for every citizen, an American approach to opioid abuse that has emphasized interdiction and incarceration over mental health treatment, the availability of licit and illicit opioids, laissez faire approaches to business regulation (hence pill mills), and long-standing ambivalence among physicians to treatment of pain. They also reflect the prevalence of the particular hopelessness that comes from denial of opportunity to people living in a country founded on hope.

All clinical studies of opioids inevitably reflect the fact that opioid treatment may not be sustained and that it may be discontinued for a variety of reasons, including lack of efficacy, adverse effects, comorbidities, drug abuse, and lack of access to alternative treatments. From an analytic point of view, these factors contribute to unexplained statistical variance.

Meta-analyses have become the generally accepted means for evaluating the large clinical trial literature, even as such analyses often do not adequately consider the scientific strengths and weaknesses of individual trials, instead focusing almost entirely on the quantitative outcomes and their susceptibility to meta-analysis. Most critically, intention to treat designs (the gold standard for RCTs) involving patients with more severe pain are either seriously undermined or precluded by high drop-out rates in placebo groups. Avoidance of these high drop-out rates requires inclusion of only patients with modest pain, who are less likely to benefit, while accommodating the limited dose titration that is possible in short duration trials (5). The particular focus on patients with modest pain is reflected in the modest doses of opioids typically employed. Of the 96 trials reviewed by Busse et al. (5), 35% involved tramadol and in the 87 RCTs for which dosing data were quantified, median milligrams morphine equivalent/day (MMED) was 45 (interquartile interval 28.2–78.3).

## THE EFFICACY OF OPIOIDS IN TREATMENT OF CHRONIC PAIN

A large number of randomized placebo-controlled trials (RCTs) have been conducted to test the efficacy of opioids in treatment of chronic non-cancer pain (5–8). Taken together, they provide evidence of modest opioid efficacy in relief of pain and improvement of physical functioning but also significant opioid side effects. Unfortunately, by and large, these trials have been marked by failure to accommodate the enormous patient to patient variability in necessary opioid dosage (see below), failure to titrate opioids to achieve adequate control of pain, over-rapid drug titration (which magnifies side effects and renders achievement and assessment of dosage adequacy difficult), and lack of recognition of the high prevalence of idiosyncratic side effects (9, 10). It may take many months to identify an opioid that is well-tolerated by a given patient, gradually titrate dosage to the point of effective control of pain, and effectively treat important comorbidities such as depression. However, among the 62 trials reviewed by Furlan et al. (6), 51% were one month or less, 39% were 5–12 weeks in duration, and the remaining 9% were 13–24 weeks in duration. There are several reports of open trials, non-randomized, involving large numbers of patients treated with either transdermal fentanyl or oxycodone continuous release that have demonstrated the ability to achieve sustained relief of pain for years (11–14). Although these trials provide some evidence of long-term efficacy and low incidence of tolerance, they cannot substitute for RCTs. In sum, few trials employing rigorous scientific methods have tested opioids as they are best used in clinical practice (15).

The challenges of testing opioid effectiveness in a way that can translate readily to clinical use can be addressed by employing an Enriched Enrollment Randomized Withdrawal (EERW) design. A 3-month trial of extended release oxymorphone for chronic moderate to severe low back pain, conducted by Hale et al. (16), involving 250 patients, is representative. During the first phase of the trial, oxymorphone was titrated to clinically optimal dosage and participants intolerant of the drug dropped out. Those stabilized on oxymorphone ($N = 143$) were then randomized to drug continuation or placebo. Physical withdrawal symptoms in those randomized to placebo were mitigated with supplementary oxycodone. By 3 months, 75% of patients in the placebo group had dropped out (53% from lack of efficacy; 11% from side effects; 11% other), compared with 30% of the oxymorphone group (11% for lack of efficacy; 10% from side effects; 9% other), thereby providing substantial evidence of efficacy. However, the high placebo drop-out rate obviated intention to treat statistical analysis of pain scores. At the end of the titration phase, 72% of patients rated their experience with the oxymorphone as good or excellent. Other EERW trials have achieved comparable results (17–20); see also review (21) and meta-analysis (22). This said, EERW trial results, in aggregate, suggest the possibilities rather than proving the case.

In addition to addressing the challenges of emulating opioid prescription in good clinical practice, EERW trials have analytic advantages and achieve greater statistical power (23). Visual analog pain scales (VAPS), the typical primary outcome measure in opioid RCTs, may be, like subjective measures in general, susceptible to anchor point drift over time (24). They also correlate poorly with more objective measures of pain, such as the McGill Pain Questionnaire (25). With an EERW design, efficacy can be established with a logistic outcome measure—participant drop-out, thereby turning to advantage the dropout

problem that plagues trials of conventional design. Drop-out may occur because of inadequate control of pain or because of opioid side effects.

Scant data are available on the distribution of opioid dosage typically needed to achieve adequate control of pain. In an EERW trial of oxymorphone for treatment of chronic low back pain involving 325 participants, Katz et al. (18) reported that 76.8% of those who successfully completed the oxymorphone titration phase ($N = 205$) achieved ≥30% pain reduction and 67.4% experienced a >50% decrease in pain; 97% rated the treatment as good, very good, or excellent. Among participants, 53% had been titrated to ≤90 mg morphine equivalent/day (MMED), 81% to ≤150 MMED, and 93% to ≤240 MMED. Maximum dose in the trial was 420 MMED [see also Rauck et al. (19)].

The RCT conducted by Krebs et al. (26), which involved 240 patients treated for chronic pain in VA hospitals, has been widely cited as proof that opioids are no more effective than non-opioid pharmacologic treatments for chronic pain. However, the mean dose of opioid was 21 MMED and only 12.6% of patients randomized to the opioid group were taking >50 MMED. Furthermore, antidepressants were among the treatment options in the non-opioid group. These study details suggest that the results of this trial may be best construed as: (1) patients whose pain is not sufficiently severe to warrant opioid treatment do not particularly benefit from opioids; or (2) opioids are not of benefit to patients with moderate to severe chronic pain when opioid dosage is not sufficiently titrated; or (3) the optional use of antidepressants in the non-opioid group substantially mitigated the inadequacy of other non-opioid therapy.

Given that further clinical trials are needed, we propose a variation on the EERW design in which initial dose is very gradually titrated and participants, rather than being randomized to drug continuation or placebo, are randomized to continuation of their opioid regimen without change or to gradual tapering, e.g., by 10%/month, utilizing control tablets containing less and less opioid—an enriched enrollment, randomized *gradual* withdrawal design (EERGW). The statistical method would be survival analysis based upon time to trial drop-out (27). This design would likely be more successful than EERW designs in sustaining participant blinding. It would enable trials extended over almost arbitrarily long periods of time and the use of Cox proportional hazards analysis to identify potential predictors of outcomes.

## ONE DOSE FITS ALL

The concept that one dose fits all has arguably been the single recommendation of the CDC that has had the greatest negative impact on patients in chronic pain, even as a number of studies suggest that the concept is not valid.

Data from EERW trials suggest 13-fold dosage variability (16, 18). These results are congruent with those of multiple studies of management of post-surgical pain in opioid-naïve patients, which have revealed an ~15-fold variability in opioid dose requirements (28–31). This experience with opioid-naïve patients suggests that dose-variability is a phenotypic phenomenon and not simply related to tolerance.

The reasons for the high variability in opioid dosage needed to achieve control of chronic pain are not well-understood. Severity of pain must be a factor. Genetic differences in hepatic metabolism can account for 3-fold or greater variability (32, 33). Genetic differences in the receptor interactions of different opioids (34) and in neural transmission also appear to be important (35, 36).

## RISK OF DEATH FROM OPIOID TREATMENT

The rise in prescription opioid-associated mortality from ~6,500/year in 1999 to 17,500/year in 2011 (37) (**Figure 1**) generated widespread concern about the risks of opioid use and paved the way for the idea that opioid over-prescribing was responsible for the opioid crisis. However, two things have been missing from this conversation: (1) the statistical contribution of increasing numbers of patients being prescribed opioids; and (2) the number of annual deaths related to prescribing by pill mills, in which opioid use is not adequately medically supervised.

It is absolute risk, not proportional risk, that matters for an individual patient and practitioner when considering a treatment (38). The estimated annual opioid-associated case fatality rate with prescription of >100 MMED is 0.25% (39) and rises to 0.5% in those receiving >400 MMED (40).

Results of epidemiologic studies are congruent with these findings. In the North Carolina study of Dasgupta et al. (41), the estimated annual mortality associated with oxymorphone (the drug with the highest associated mortality) was 0.54%/year. In this study, annual mortality rose more or less linearly with opioid dose (without an inflection point), reaching a maximum of 0.80% (95% CI 0.55–1.10) at 650 MMED. This study could not distinguish between deaths associated with opioids prescribed chronically for treatment of chronic pain and deaths associated with "one-off" prescriptions obtained by opioid abusers on the other. Only 51% of decedents had an active opioid prescription on the day of death and 24% had no record of being dispensed an opioid in the prior year, a finding replicated in other studies (42, 43).

It may be challenging to distinguish mortality related to opioids *per se* from mortality associated with opioids and conditions under which they are prescribed (in which case, to one extent or another, opioid prescription may be simply a marker of disease and condition) (see also below: Morbidity and mortality associated with chronic pain). Agnoli et al. (44) assessed *all-cause* mortality among 90,622 participants in the Medical Expenditure Panel Survey according to whether patients had received no opioids, 1–5 opioid prescriptions, or six or more opioid prescriptions during the first year of 2-year study epochs. In the unadjusted analysis, there was a strong association between opioid prescriptions and mortality. However, this association disappeared when the analysis was adjusted for socio-demographics, health status, and health care utilization.

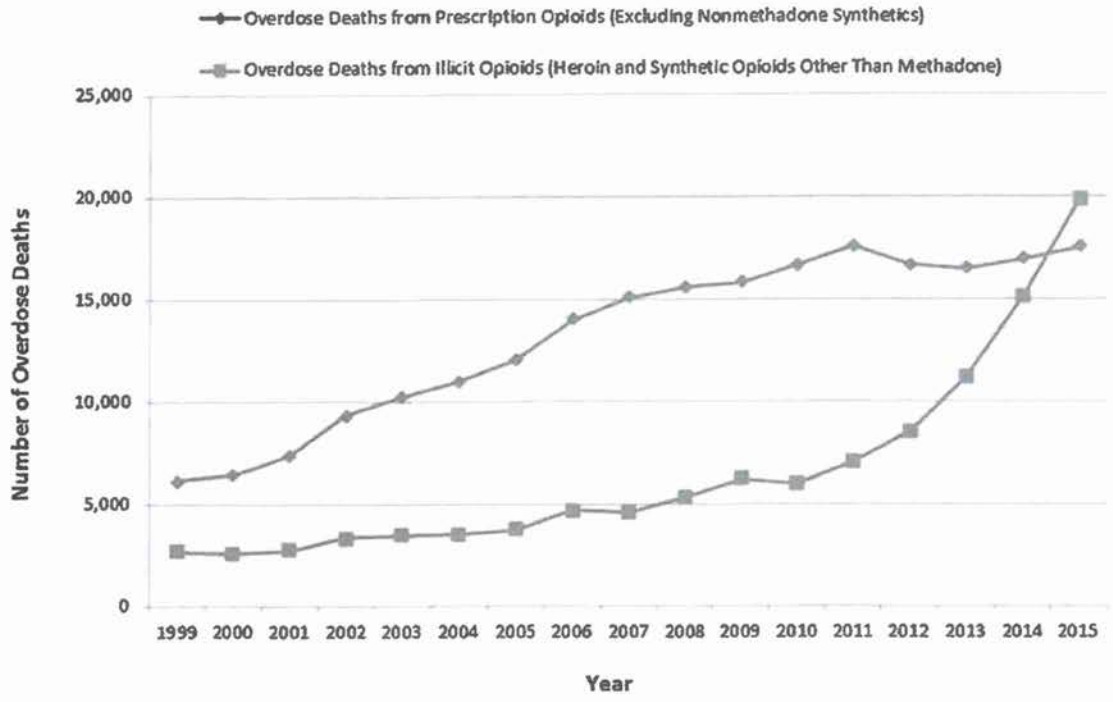


**FIGURE 1 |** Number of overdose deaths from prescription and illicit opioids, United States, 1999–2015 (37).

The prevalence of chronic pain, coupled with these case fatality rates, poses what may be a unique conundrum for medicine and public policy. If there were 10 million Americans with chronic pain who required opioid dosage of >100 MMED to achieve adequate pain control, this would translate to an annual mortality of 25,000. What may be acceptable to the patient and constitute responsible individualized treatment of a serious health problem by a physician thus may scale up to an issue that intrinsically warrants national concern.

Almost certainly, prescription opioid case fatality rates, however modest, could be further reduced by better training of physicians (45), more complete eradication of pill mills and black-market sources of opioids, reduced prescription-opioid diversion, better ascertainment and treatment of comorbid depression, reduction of all too frequent concurrent abuse of alcohol (46), and a better understanding of why overdoses occur (47).

The data reviewed here on opioid benefits, however incomplete, and risks provide the basis for opioid treatment decisions based upon a careful weighing of benefits against risks, as with medical decision making in general. In medical practice, we commonly weigh risks and benefits that are comparable to those associated with chronic opioid therapy. For example, the case-fatality rates associated with >100 MMED opioid therapy are comparable to the risks of fatal bleeding associated with use of rivaroxaban (0.2%/year) and warfarin (0.5%/year) in the prophylaxis of stroke due to atrial fibrillation (48). This might be considered an inapt comparison. However, systemic anticoagulation for atrial fibrillation is recommended for $CHA_2DS_2$-VASc scores of $\geq$2 (49), which corresponds to an annual stroke risk of $\geq$2.2% (50). The 5-year likelihood of being stroke free in a patient with the 2.2% annual stroke risk is 89.5%. On the other hand, the patient with moderate to severe chronic pain experiences suffering and disability from the outset.

## PREVALENCE OF OPIOID USE DISORDER

Opioid use disorder (OUD) is thought to be prevalent among patients prescribed opioids (51). The extent to which clinicians make the diagnosis of OUD on the basis of perception of suspicious behavior, e.g., requests for increased opioid dosage to ease pain ["pseudo-addiction" (52, 53)], as opposed to DSM criteria, is unknown, and diagnoses based solely on clinician judgment must therefore be questioned. The prevalence of pseudo-addiction warrants further study. Vowles et al. (54), in an oft-cited study, reviewed a carefully selected 38 papers from a total of 367 identified in the literature. These papers reported rates of misuse of 0.08–81% (1,012-fold variability), abuse of 8% (data provided by one study) and ostensible addiction of 0.7–34.1% (48.7-fold variability). Incidence of iatrogenic opioid abuse (ICD-9 or DSM-4 criteria) is lower in studies of higher quality; studies using ICD-9 criteria compared with DSM-4 criteria; the use of strong opioids; and with prescriptions of $\geq$ 3 months duration (55). Other reviews, for example that of Fishbain et al. (53), which included 67 studies, revealed variability between

studies comparable to that reported by Vowles et al. a mean rate of ostensible addiction of 3.27%, and a complicated and nuanced picture of opioid use and misuse in patients on opioid therapy for chronic non-cancer pain.

The enormous variability in results reported by Vowles et al. (54) raises questions about the validity and reliability of the outcome measures. The definitions of the outcome measures provide some clues to potential sources of the variability. Misuse was defined, according to widely accepted criteria, as opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects. This definition could be applied in several ways unrelated to abuse: patient use of the opioid at times of the day at odds with those recommended by the prescriber, taking extra pills of short acting drugs on bad days and less than the prescribed amount on good days (pain may fluctuate substantially from day to day), urine drug screens that were either falsely positive or turned up marijuana use, requests for an increase in opioid supply to cover inter-current surgery, accidents (however rare), or single instances of use of a different opioid diverted from a family member. We suggest that in good clinical practice, a judgment of misuse should hinge on patterns of behavior extending over repeated clinic visits. Addiction was defined by Vowles et al. (54) as "impaired control over drug use, compulsive use, continued use despite harm, and craving." Addiction is an extraordinarily complex disorder and is operationally very difficult to define (56). A diagnosis of addiction could be correct. However, practicing clinicians are rarely in a position to apply DSM criteria for addiction in a fully informed manner. We suggest that in the present US regulatory environment, "potential for harm" may be as much in the eye of the prescriber or the pharmacist as in any observable behaviors of the patient. Physician concern is often dosage-related [e.g., >90 MMED since CDC 2016 (1)]. "Compulsive" use might simply reflect the severity of the pain and the inadequacy of pain control. "Craving" might actually reflect pseudo-addiction—the patient craves higher doses because pain control is inadequate.

A very different type of analysis of the prevalence of OUD by Han et al. (57), based on data from the 2015 National Survey on Drug Use and Health (NSDUH) is revealing. The sample consisted of 78,976 respondents aged 12 years or older living in households or non-institutional group housing who were representative of non-elderly US adults in 2015–2016. Data on sensitive questions were obtained through a computer driven audio interview arranged to assure anonymity. Weighted estimates suggested that 91.8 million (37.8%) of U.S. civilian non-institutionalized adults used prescription opioids over the prior year. Of these, 12.5% reported opioid misuse (use other than as directed by a physician) and 2.1% opioid abuse (defined as meeting ≥1 of four DSM-4 abuse criteria). Relief of pain was reported as the most common reason for opioid misuse (66.3%) and opioid abuse (48.7%). Among respondents who reported misuse or abuse, opioids were most often obtained from a physician (35.1 and 44.3%, respectively) or a friend or relative (53.1 and 35.9%) and were uncommonly obtained from a stranger or drug dealer (3.1 and 13.8%). The study by Han et al. suggests that opioid abuse is relatively rare among patients prescribed opioids (2.1%) and in 48.7% of cases, search for pain relief is the major driving factor.

Use of non-prescription opioids to medicate a health problem is strongly negatively correlated with ultimate heroin use (58). Boscarino et al. (59), in a large interview survey of a clinic population, reported a *lifetime* prevalence of mild OUD [2–3 DSM-5 symptoms (60)] of 28.1%, moderate OUD (4–5 symptoms) of 9.7%, and severe OUD (6+ symptoms) of 3.5%. It is worth noting that item 1 of the DSM-5 criteria (use of opioids in larger amounts or over a longer period than intended) would likely be endorsed by a large percentage of patients treated for chronic pain. For items 2 (persistent desire or unsuccessful efforts to cut down), 3 (a great deal of time spent in activities necessary to obtain the opioid), 4 (craving or strong desire to use opioids), and 7 (important social, occupational, or recreational activities are given up or reduced because of opioid use), responses could easily reflect a conflation of opioid effects with the effects of pain, desire to alleviate pain, activities involved in getting treatment for pain, or activities forgone because of persistent inadequately controlled pain. In a large survey of a clinic population, among participants who acknowledged only 2–3 symptoms (mild OUD), 33.7% endorsed item 1, 88.1% item 2, 44.7% item 4, and 23.8% item 7 (61). These data suggest a need to refine our operational measures of OUD [see Fishbain et al. (53) for extended consideration of this issue].

## THE GATEWAY THEORY

Up to 80% of patients reporting at least one past episode of heroin use also report at least one prior *nonmedical* use of prescription pain relievers (62). The word "non-medical" is often lost in discussion and the conclusion drawn that prescription of opioids, however brief, carries a high risk of leading to OUD and thus, constitutes a gateway to drug abuse. Acceptance of the gateway theory has also added fuel to the argument that many patients who are prescribed opioids are taking them because of OUD and not pain.

Several large studies refute the gateway theory. Brat et al. (63) reported a retrospective study based on insurance records of 1,015,116 opioid naïve patients undergoing surgery, 56% of whom received post-operative opioids. In the course of follow-up, 0.6% received a clinical diagnosis of opioid abuse during an average follow-up of 2.5 years. Likelihood of a diagnosis of opioid abuse was 0.15% among patients provided an opioid prescription for <1 week and rose to asymptotically approach 2% in patients prescribed opioids for >13 weeks. It is plausible that ongoing pain, rather than OUD, led to ongoing patient requests for opioid prescription renewals (pseudo-addiction), particularly given that the prevalence of persistent pain 6 months after surgery has been reported to be as high as 29.5% with some surgical procedures (64).

Sun et al. (65) reported a retrospective study of 641,941 opioid-naïve patients undergoing 11 common surgical procedures, including total knee arthroplasty (TKA), total hip arthroplasty, laparoscopic or open appendectomy, laparoscopic or open cholecystectomy, Cesarean section, sinus surgery,

transurethral resection of the prostate, and simple mastectomy. The 1-year incidence of chronic opioid use (defined as 10 renewed prescriptions or 120 days of continuous use within 1 year) ranged from 0.09% for Cesarean section to 1.41% for TKA. The reported incidence of chronic opioid use in non-surgical patients was 0.136%. Shah et al. (66) reported a retrospective study of 675,527 patients who had undergone urologic surgery. Within the subsequent year, a documented clinical diagnosis of opioid dependence or overdose (i.e., without reference to DSM criteria) was made in 0.09%.

These studies, involving a total of 2,332,584 patients, suggest that the risk of long-term persistent use of opioids, or of clinically diagnosed abuse, following treatment for acute perioperative pain, is extremely low. They also provide no support for constraining the short-term use of opioids in the treatment of acute pain.

Two recent studies provide a different picture. The study of Shah et al. (67) involved 1,294,247 patients randomly selected from the IMS Lifeline+ database, which is representative of the US commercially insured population. Among persons prescribed opioids for at least 1 day, the probability of continued opioid use at 1 year was 6.0% and at 3 years, 2.9%. However, because this study involved all patients prescribed opioids and not just those prescribed opioids for a particular medical event, e.g., surgery, it was likely to have included patients with chronic pain whose opioid therapy happened to be initiated during the study interval. Indeed, those maintained on opioids for >1 year were more likely to be older, female, and to have a pain diagnosis before opioid initiation. It also appears that as few as two opioid prescriptions could have defined "continued opioid use" in this study (68).

Brummett et al. (69) reported a retrospective cohort study of 31,177 patients in the Clinformatics Data Mart who underwent major or minor surgical procedures and had not received opioids during the prior year. The primary outcome measure, "new persistent opioid use," was defined as the filling of one or more opioid prescriptions between 90 and 180 days after surgery by patients who had received a perioperative opioid prescription. Of those undergoing minor surgery, 5.9% met the outcome criterion, whereas of those undergoing major surgery, 6.5% met the criterion. History of back pain, neck pain, arthritis, anxiety, depression, or alcohol or substance use were independently associated with opioid use. Whether or not the filling of as little as one opioid prescription between 90 and 180 days after surgery should be a source of medical concern is unclear. The impact of opioids on pain other than that due to surgery could have informed some patients of their effect on other painful conditions.

Finally, in a systematic review and meta-analysis of 33 studies involving 1,922,743 individuals [which included the Sun et al. (65), Shah et al. (66), and Brummett et al. (69) studies], Lawal et al. (70) found an overall risk of chronic opioid treatment after surgery of 6.7%. However, when the analysis was restricted to opioid-naïve patients, the rate was 1.2%. The major statistical predictors of chronic opioid treatment were pre-operative opioid use, back pain, fibromyalgia, depression, and anxiety.

In summary, the major studies of long-term opioid use after surgery are in substantial agreement that long-term post-surgical rates of opioid use are very low (1% or less), taking into account some variability in the definition of what constitutes extended opioid use and the nature of the surgery. Chronic pain related to pre-existing conditions or to sequelae of surgery are just as plausible as OUD as a potential explanation for long-term opioid use after surgery, although this matter requires further study. One important weakness of the cohort studies we have described is that they cannot tell us how many patients prescribed short-course opioids for medical reasons "went off the grid" and obtained further opioids from illicit sources. This is a difficult population to study and to gain insights requires studies like that of Winkelman et al. (71) (see below: Who are the victims of the opioid crisis?).

## MORBIDITY AND MORTALITY ASSOCIATED WITH CHRONIC PAIN

The intended and unintended effects of the CDC guideline have created a second crisis, this one involving patients in chronic pain (2). Epidemiologic studies suggest that 22% of U.S. adults (55 million) experience chronic pain (3). In any given year, 14.3% of insured adults have pain sufficient to lead to an opioid prescription (3% for >90 days) (72). The corresponding figure for Medicare Advantage patients is 25.7% (7% for >90 days) and for disabled Medicare patients 51.5% (14% for >90 days).

The health-related quality of life of patients with chronic pain is comparable to that of patients dying with cancer (73). Inadequate treatment of chronic pain is associated with increased functional limitations, reduced employment, increased absence from work, disability retirement, reduced household income, poor global recovery from surgery, worsened mental health, increased use of health care resources, increased mortality (3, 74, 75), impaired cognitive function (76), and brain atrophy (77). Chronic pain is associated with increased risk of suicidal ideation, planning, and attempts (78, 79), even after control for psychopathology (80). Chronic post-operative pain impacts activities of daily living in ~25% of patients a year after undergoing inpatient orthopedic surgery (81). Inadequate pain relief after surgery is associated with increased length of stay, re-admission rates, and time to ambulation (64). In 2011, the Institute of Medicine estimated that the annual cost to society of chronic pain, including post-operative pain, was $560–635 billion (82), based on estimated health care expenditures and costs of lost productivity. Treatment of pain has been associated with improvements in activities of daily living, reduced depression or improved mood, reduced fatigue, improved sleep, improved level of function, increased ability to work, increased enjoyment of life, and improved quality of life (3).

These considerations are germane to studies that seek to determine if chronic opioid use is associated with excessive morbidity or mortality. Patients prescribed opioids are likely to differ from those prescribed alternative treatments, pharmacologic or non-pharmacologic, for chronic pain in two ways: (1) they are receiving opioids, and (2) they have more severe pain. If more severe pain is eventually sufficiently mitigated with titrated opioid treatment, then theoretically,

mortality attributable to inadequately treated pain should decline with time. Ray and colleagues (83) reported a retrospective study of 45,824 Tennessee Medicaid enrollees, contrasting the mortality associated with treatment with long-acting opioids with that associated with non-opioid analgesics. It provides some support for this hypothesis: the hazard ratio for death during the first 30 days of long-acting opioid prescription was 4.16 but it declined over time to 1.03 in patients on these drugs for >180 days.

Mechanisms of death associated with chronic pain, with or without opioid treatment, have not been adequately studied. They could include cardiovascular events (83) related to stress and heightened sympathetic tone, opioid effects on the heart (83), pulmonary embolism linked to physical inactivity, suicide, and death from overdose of illicit drugs. More generally, comparative cohort studies, even those employing propensity matching [e.g., Solomon et al. (84)] are likely to conflate effects of treatment (e.g., opioids vs. NSAIDS) with effects of disease (more vs. less severe pain) unless the cohorts are adequately matched for pain severity, something impossible to do in retrospective studies.

## EFFECTIVENESS OF NON-PHARMACOLOGIC TREATMENTS

The first of the CDC's 12 recommendations for treatment of chronic non-cancer pain was "Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred" (1). This statement implies that there is evidence that (1) non-pharmacologic therapies are beneficial for chronic non-cancer pain, and (2) the balance of benefit and risk for these therapies is superior to that achieved with opioids. The benefits and risks of opioid therapy were reviewed above and the risk of harm with non-pharmacologic therapies is likely to be low. Therefore, we will focus on the issue of effectiveness of non-pharmacologic therapies.

In 2018, the Agency for Healthcare Research and Quality (AHRQ) systematically reviewed the literature on non-pharmacologic therapies (85); 4,996 candidate trials were considered and ultimately, 218 publications (representing 202 RCTs) that met quality criteria were analyzed in detail. Most enrolled patients had at least moderate baseline pain intensity (>5 on a 0–10 scale). Most trials reported only short-term outcomes. Treatment was compared with usual care or sham therapy. Treatments reviewed included yoga, tai chi, qigong, spinal manipulation, acupuncture, laser therapy, ultrasound, exercise, massage, multidisciplinary rehabilitation, psychological therapies, cognitive behavioral therapy, mindfulness-based stress reduction, and the Alexander technique for mindful reduction of tension. The strength of the medical evidence, with few exceptions, was graded as low. To the extent that any of these therapies had an effect on pain or level of function, most effect sizes were small. None of the reviewed papers were from Phase III trials. A 2020 AHRQ update did not reveal any important new findings (86). A recent retrospective analysis assessed the impact of massage, acupuncture, and chiropractic care administered over 3 years in a population of 309,277 veterans with chronic musculoskeletal pain, 7,621 of whom received one or more of the therapies (87). There was no significant difference in the self-rated pain intensity outcome between those who were treated and those who were not.

However, we suggest that there is a more fundamental problem with the CDC recommendation: sound scientific grounding for this recommendation would require conducting comparative effectiveness trials. Given the results discussed in the foregoing, it seems unlikely that non-pharmacologic therapies will ever achieve the level of effectiveness needed to justify their use as a sole treatment for moderate to severe chronic non-cancer pain. Rather, their value may lie in their ability to complement pharmacological therapy (including opioid treatment) and thereby reduce drug dosage. The results of 60 small studies (88), almost all targeting short-term treatment of pain, provide some support for this concept. The effectiveness of non-pharmacologic therapies could be tested with a variant of the EERGW design discussed above. Opioid dosage would be gradually reduced to the extent possible in *both* groups. The statistical analysis would compare ultimate opioid dosage in the drug + non-pharmacologic therapy group with that of the drug only group.

## SIMULTANEOUS USE OF OPIOIDS AND BENZODIAZEPINES

The CDC guideline (1) proscribes the concurrent use of opioids and benzodiazepines. Two studies warrant particular attention. Sun et al. (89) conducted a case-cohort analysis of 315,428 patients in the Marketscan database (Truven Health Analytics, Ann Arbor, MI) who filled at least one prescription for an opioid between January 1, 2001 and December 31, 2013. The adjusted odds ratio for an emergency room visit or hospital admission for ostensible opioid overdose among those using both classes of drug was 2.14. Unfortunately, this impressive study suffers a serious methodological weakness: the gold-standard diagnosis derived from physician judgment, not response to naloxone treatment. The alleged risks of concurrent use of these two drug classes have been sounded for many years despite the absence of adequate data. The very fact that a patient is taking the combination may alter the diagnostic evaluation of and the attribution of cause for altered mental status (90). Thus, it is possible that in many patients included in the study by Sun et al., the mere discovery that a patient was taking both an opioid and a benzodiazepine increased the likelihood of a diagnosis of opioid overdose. Consistent with this hypothesis, the diagnosis of opioid overdose related to the combination was made twice as often in 2013 as it was in 2001.

In a case-cohort study, Park et al. (91) analyzed opioid-associated mortality rates in 420,386 veterans prescribed opioids, 27% of whom had concurrent or past prescriptions for benzodiazepines [ssee also Xu et al. (92)]. The past prescription cohort was included in an attempt to control for excess mortality associated with underlying conditions, such as chronic anxiety disorder, post-traumatic stress disorder, and depression, for which benzodiazepines are commonly prescribed and in which

drugs are more commonly misused. The adjusted hazard ratio for death in the prior prescription group was 2.33 and in the current prescription group, 3.86. It was elevated for all benzodiazepines except temazepam. Hazard ratio increased with increasing opioid dosage and increasing benzodiazepine dosage. Because of the challenge of controlling for the differences between the benzodiazepine and non-benzodiazepine cohorts, the authors concluded: "benzodiazepines might be better conceptualized as a marker of risk with unknown direct causal links to death from overdose." Dasgupta et al. (41), in a population-based cohort study of all North Carolina residents, reported a 10 times elevated risk of death associated with the presence of both opioids and benzodiazepines at time of death. However, 49.6% had no active opioid prescription at the time of death, suggesting that in half of the cases, illicit or diverted drugs must have played a role. Therefore, benzodiazepines could have either contributed to risk of death or simply been a marker for polysubstance abuse.

Zedler et al. (93) reported a case-control study (10 controls/case) of 817 VA patients who experienced either opioid overdose or serious opioid-induced respiratory depression. They did identify benzodiazepines as a risk factor (RR 1.49) but also found that antidepressants were actually a greater risk factor (RR 1.98). These findings are consistent with the conclusion of Park et al. (91) that benzodiazepines are best viewed as a marker of risk with unknown direct causal links to the outcome measure.

From these studies, we conclude that calculating the additional risk posed by co-administration of benzodiazepines with opioids poses a major scientific challenge and currently available data can best be considered as suggestive of a modest increase in risk (relative risk ~2), at least part of which may be attributable to concurrent disease rather than the drug combination.

Finally, the CDC guideline did not consider the prevalence and negative impacts of idiopathic insomnia and anxiety disorders or the paucity of effective and safe alternative treatments for these two disorders.

## THE RELATIONSHIP OF DEPRESSION TO CHRONIC PAIN AND ITS TREATMENT

Between 30 and 54% of people with chronic pain also have major depressive disorder (MDD) (94). Patients with moderate to severe pain have a more than 2-fold increase in the risk of developing a mood or anxiety disorder (95). General practitioners detect on average 50% of cases of depression (96). Rates of depression reported in large opioid database studies range from 12.9 to 32% (97, 98), suggesting that depression is also commonly missed in patients being treated for chronic pain. Diagnosed depression is often untreated or under-treated (99).

As Braden et al. (100) put it, "It is possible that opioids prescribed to depressed persons may be treating an undifferentiated state of mental and physical pain." If depression can be viewed as an amplifier of suffering related to pain, then successful treatment of depression might be expected to reduce chronic pain and reduce opioid dosage (a hypothesis testable in a trial employing an EERGW design).

Among patients with chronic pain, inadequately treated depression is associated with a number of adverse outcomes. Patients with depression are three times as likely to be prescribed opioids as those without (100). Among 10,311,961 patients who received short term opioid treatment of pain, depression was associated with a doubling of the hazard ratio for long-term opioid use (101). Patients with depression who are prescribed opioids for non-cancer pain are likely to receive higher doses (100, 102). MDD is associated with a higher prevalence of alcohol use disorders (103) and of opioid misuse and OUD (57, 104). Patients with comorbid non-cancer pain and depression have higher pain interference with activities of daily living and higher mental distress (100). These studies, in aggregate, suggest that aggressive treatment of depression, in addition to its salutary effects on pain management, might mitigate many of the most troublesome issues associated with treatment of chronic pain in patients with comorbid depression.

## THE CAUSES OF THE OPIOID CRISIS

The trends evident in **Figures 1, 2** suggest that the opioid crisis has been defined by two separate epochs, the first, which might be termed the "*prescription epoch*," extending from 1999 to 2011, and the second, which be might termed the "*illicit epoch*," extending from 2012 to the present. Many efforts to address the opioid crisis, including those by the CDC (1), appear to have conflated the operative mechanisms in these two epochs (107), even as the CDC now explicitly recognizes them (108).

Deaths attributed to prescription opioids steadily increased from 6,500 in 1999 to 17,500 in 2011 and have since remained fairly stable. Deaths from illicit opioids roughly doubled between 1999 and 2011, from ~3,000 to 7,000, but were still far outnumbered by deaths associated with prescription opioid use. However, between 2011 and 2015, during the period when mortality from prescription opioids remained stable, deaths from illicit opioids increased from 7,000 to 20,000 and they have continued to rise since (**Figure 1**). In 2019, there were 49,860 opioid deaths, 13,501 (27%) from prescription opioids and 36,359 (73%) from illicit opioids (109). Opioid prescribing rates peaked in 2012 and have steadily declined since (**Figure 3**), providing further evidence that prescription practices and deaths from illicit opioids are not linked.

However, the CDC hypothesis is that the opioid crisis has been and still is being driven by excessive prescribing rates. We tested this hypothesis by using state by state data provided by the CDC on prescription rates (110) and mortality (111) (**Figure 4**). The hypothesis received no support from these data: higher prescription rates were actually associated with lower mortality rates but the adjusted $r^2$ was only 0.015 and there was not a significant probability that the slope was different from zero.

We tested the CDC hypothesis in another way, identifying, state by state, the year of maximal opioid prescribing between 2006 and 2017, which in nearly all states was between 2010 and 2014 (111). We then subtracted the 2017 prescription rate from the rate for that peak year and tested whether

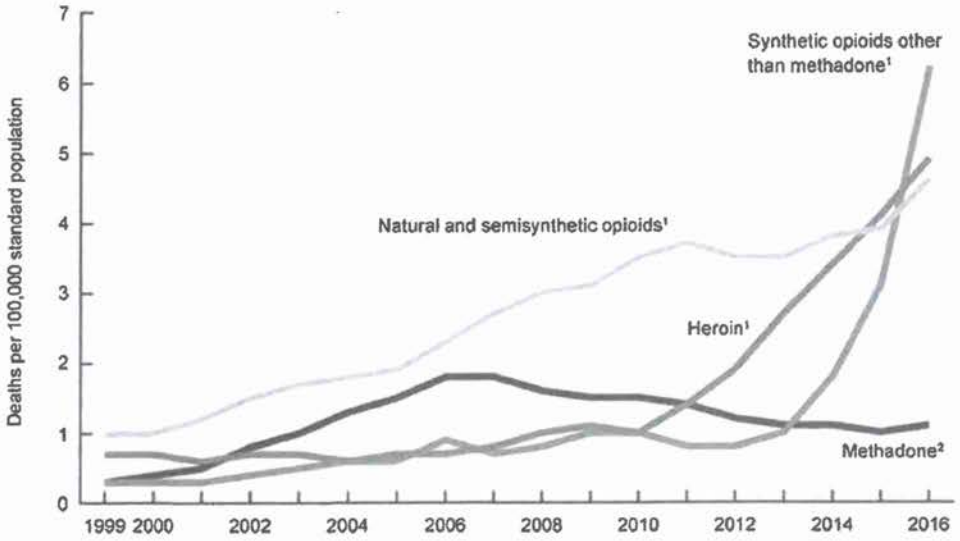


**FIGURE 2 |** Age-adjusted drug overdose death rates by opioid category, United States 1999–2016 (105). The category of synthetic opioids corresponds almost entirely to fentanyl. A Massachusetts study determined that 96% of this fentanyl was illicitly manufactured (106).

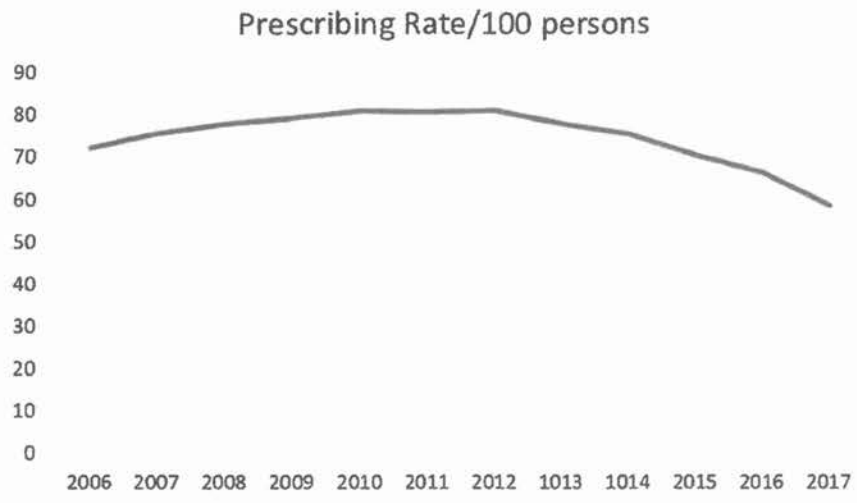


**FIGURE 3 |** United States annual opioid prescriptions rates/100 persons (110) (CDC data).

this difference correlated with changes in mortality over the same time period (108) (**Figure 5**). The greater the decline in prescription rates, the greater the *increase* in mortality rates. The adjusted $r^2$ was 0.132 and there was a significant probability that the slope was non-zero ($p = 0.00596$). Statistical association is not causation, these are multidimensional issues, and there may be other explanations. Nevertheless, if opioid over-prescription has been driving the crisis since 2012, then there should be a correlation between prescription and mortality rates and curtailing prescriptions should be reducing morality; the evidence presented here, derived directly from CDC data, suggests that neither is the case.

If mainstream opioid prescription practices have not propelled the increase in opioid mortality since 2011, then what has? The answer appears to be well-intended efforts by the states to curb pill mills and the ready availability of pure and inexpensive Mexican heroin and Chinese fentanyl, likely complemented by use of opioid pills diverted from other users or obtained from black market sources. Remaining pill mills, aided by the major drug distribution firms that supply them (112),

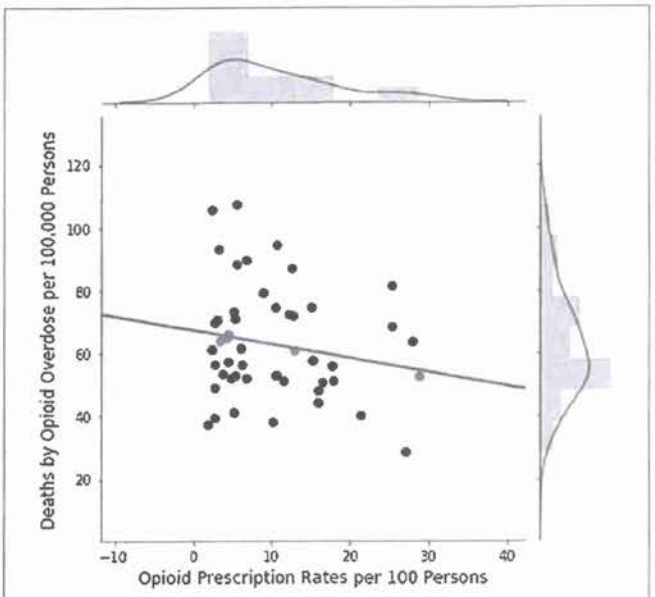


**FIGURE 4 |** Opioid mortality rates by state in 2016 (111) in relation to number of opioid prescriptions by state (110) (CDC data). Opioid mortality rates are based on ICD codes for narcotic related (T40.0–T40.6) intentional and unintentional drug overdose deaths (X42, X62). Opioid prescriptions accounted for 1.5% of the variance in opioid mortality. The slope of the regression line is not significantly different from zero ($F = 1.744$, $p = 0.193$).

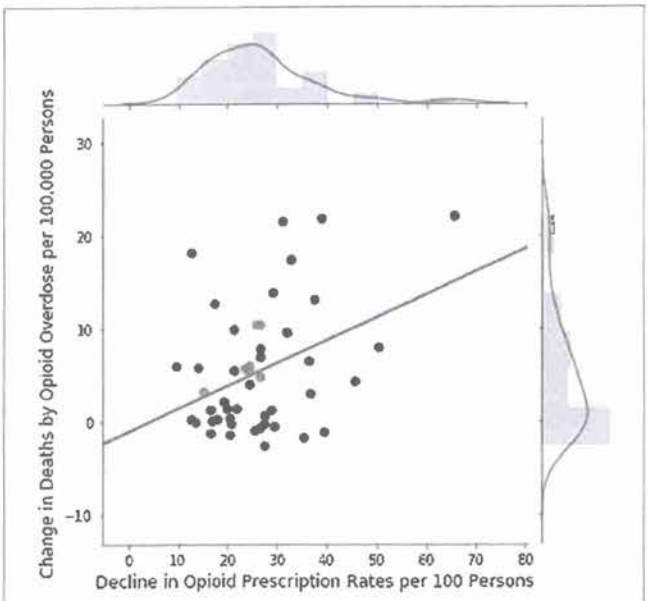


**FIGURE 5 |** Changes in mortality rates by state (calculated as in **Figure 4**) between the year of maximal prescription rate and 2017 (111) in relation to the decline in opioid prescription rates from their maximum in the 2006–2016 epoch to 2017 (110) (CDC data). The model accounted for 13% of the variance. The slope of the regression line is significantly different from zero ($F = 8.298$, $p = 0.00596$).

are likely to be an additional factor. What these sources have in common is that they result in use of opioids in the absence of close medical supervision. The evidence is circumstantial but compelling (62, 107, 113–115). Recent data also suggest that an increasing percentage of deaths attributed to prescription opioids likely involves patients who supplemented prescription opioid regimens with heroin and/or fentanyl (115).

There are remarkably little statistical data on pill mills. In fact, one can only infer their prevalence and output from CDC state maps of prescriptions/100 persons (110). Nonetheless, it appears that pill mills were responsible for flooding much of the country with large supplies of prescription opioids, likely starting in the late 1990s (116). It also seems likely that it was the aggressive promotion of Oxycontin (which was FDA licensed in 1996) by Purdue Pharma that made the early phase of the national opioid crisis (2000–2012) more of an Oxycontin crisis than a morphine, hydromorphone or fentanyl crisis.

Because the use of drugs distributed by pill mills was not closely supervised medically, misuse, diversion, and addiction appear to have become prevalent, both in states with large pill mill distributions and in areas of the country that were most susceptible to the lure of opioids because of poverty, mental illness, hopelessness, and a complex of other factors (117). Deaths from pill mill prescribed drugs also likely made a substantial, albeit incalculable, contribution to the rising mortality from prescription opioids between the late 1990's and 2012. Unfortunately, because state efforts to reign in pill mills came late, by 2012, the population of people who were misusing or were addicted to prescription opioids had grown to substantial proportions. In a 2007 study of 27,816 individuals entering addiction treatment programs, 78% of those who reported use of Oxycontin also reported that the drug had not been prescribed for any medical reason (118). As pill mill crackdowns became more prevalent, these people either could not obtain prescription opioids or could no longer afford them. The introduction of an abuse-deterrent formulation of Oxycontin in 2010 may also have been a factor (62). In states with the highest initial rates of Oxycontin misuse, the introduction of the abuse-resistant formulation was associated with the largest differential increases in heroin deaths (119).

The pill mill crackdown and the introduction of abuse-resistant Oxycontin brought the prescription epoch to an end. The introduction of inexpensive and easily available high purity heroin and fentanyl, often in combination, appears to have then ushered in the illicit epoch, playing a major role in increasing unsupervised opioid use and associated mortality (58, 62, 120). Heroin use has always been dangerous but, because of the 50 times greater potency of fentanyl and the unpredictable amount of lacing of heroin with fentanyl, heroin use has been converted from merely dangerous to something akin to Russian roulette, hence the continued and accelerating climb of opioid deaths since 2011.

In summary, one would not have expected a strategy to control the opioid crisis to be effective when it consisted of restriction of physician prescribing practices in a crisis actually caused by pill

mills, black market opioids, and street heroin and fentanyl. The evidence suggests that indeed, this has been failed approach.

## WHO ARE THE VICTIMS OF THE OPIOID CRISIS?

Because the people caught up in the crisis live substantially off the medical grid until they die, it is difficult to know exactly who they are. However, a recent study (71) has provided a great deal of information about this population. Winkelman et al. analyzed data from the 2015–2016 NSDUH sample (see above, Prevalence of Opioid Use Disorder). Of the sample, 23,452 (29.7%) interviewees had used prescription opioids, 3,913 (4.95%) reported prescription opioid misuse, 648 (0.82%) prescription abuse (defined by DSM-4 criteria), and 451 (0.57%) heroin use. The misuse/abuse/heroin use population was preponderantly male (respective percentages in the three groups 54.2, 58.9, and 66.9); white (65.8, 72.9, and 72.3%); aged 34 or less (particularly the heroin users); high school or less educated; single (63.9, 68.4, and 85.7%); without children; had income below twice the federal poverty level; and listed themselves as unemployed or other. These individuals were more likely to report fair or poor health (15.5, 24.9, and 17.6%); a chronic health condition; any disability (22.5, 35.7, and 26.0%); and impairment of mental health (particularly in abuse and heroin use groups). They were 3–4 times as likely as non-opioid users to report alcohol dependence or abuse (19.2, 25.6, 16.2%). They were far more likely to use other drugs, including sedatives, tranquilizers, stimulants, hallucinogens, inhalants, methamphetamine, cocaine, or marijuana (68, 82.7, and 92.9% reported use of one or more).

These use data fit quite well with data on annual age-specific opioid-related overdose mortality, bearing in mind that overdose-related mortality is complex, multiple drugs are commonly implicated in any given death, assay of some drugs is complicated and may be beyond the capabilities of individual medical examiners, and death may not be accurately attributable to a single drug, or even be due to drugs. Between 2012 and 2017, mortality rose from 8 to 18/100,000/year in the 15–24 age group; 7.7–16.8 in the 25–34 age group; 9–15 in the 35–44 age group; 5.3–10.8 in the 45–54 age group; 1.2–2.2 in the 55–64 age group; 0.6–0.8 in the 65–74 age group; and 0.5–0.7 in the 75–84 age group (111). Thus, the age groups most likely to be *prescribed* opioids for chronic pain, seniors over age 55 (121), and that likely benefited the most from the liberalized opioid prescription policies of the 1990 s and early 2000's, experienced low mortality rates and a small absolute increase in opioid-overdose related mortality, whereas mortality was high and rose rapidly among younger people who are infrequently prescribed opioids for longer than a few days.

A complex array of factors contributes to opioid abuse (113), including poverty, lack of opportunity, substandard living and working conditions (and the contribution of job-related injury to pain and downward mobility), unstable housing, imprisonment for drug-related offenses, childhood adverse experiences, poor physical and mental health, social isolation, and the development of hopelessness and despair—all quite congruent with the data of Winkelman et al. (71). The age patterns of opioid use cited above suggest that young people are particularly likely to respond to these factors with opioid abuse.

## IMPACT OF CDC 2016 GUIDELINE ON HEALTH CARE PROVIDERS

The CDC guideline issued in 2016 (1) was ostensibly intended to guide the opioid prescribing practices of primary care physicians. The mechanisms underlying their actual effect appear to have escaped serious scrutiny as we have been unable to find any systematic studies [however, see (107)]. Nevertheless, it is our impression that the guideline has achieved its greatest impact by convincing health care provider organizations that violations of the guideline by their member physicians may increase organizational liability exposure (114). Because suspension of clinical privileges—a catastrophic outcome for individual physicians—can be easily accomplished, limitation of prescription dosage, and even participation in comprehensive pain management is under near absolute control by these organizations. In addition, by mid-2017, 23 states had passed laws limiting prescription duration or dose or authorizing other entities to set limits with effective legal force (122). In all but four of these states, these laws were limited to prescriptions for acute pain. However, we suggest that this intrusion of state legislatures into pain management may have further reduced the willingness of physicians to provide comprehensive pain management. Of note, in June 2020, The American Medical Association (123) publicly suggested that the CDC guideline could be substantially improved by the urging of state legislatures, payers, pharmacy chains, pharmacy benefit management companies, and all other stakeholders to immediately suspend use of the CDC guideline as an arbitrary policy to limit, discontinue or taper a patient's opioid therapy.

## CONCLUSIONS

This analysis of the clinical scientific literature on opioids suggests that many of the conventional assumptions about opioids, including safe opioid dosage, opioid efficacy, the factors that lead to opioid use and abuse, and the risks associated with opioid use, are not supported and in many cases, are refuted by existing scientific data. Conclusions about opioid efficacy, or the lack thereof, have been drawn from seriously flawed RCTs characterized by inadequate experimental designs. Data on the high variability in opioid dosage requirements and the high frequency of idiosyncratic side effects have been overlooked. Estimates of the risk of death from prescription opioids have been largely predicated on the national increase in total opioid mortality from all sources, legal and illegal. Well-designed studies have demonstrated estimated annual case fatality rates for >100 MMED regimens in the vicinity of 0.25%/year—a level of risk comparable to that associated with chronic anticoagulation for prophylaxis of stroke due to atrial fibrillation. Excess risk of death associated with opioid use conflates risks attributable to

opioids and risks related to being in chronic pain, with its associated comorbidities. Risks of the development of OUD have commonly been overestimated, even as the operational definition of OUD requires further research. State legislatures are passing laws based on the gateway theory even as scientific evidence has demonstrated that this theory has little merit.

Strong measures are being taken to restrict prescription opioid use without consideration of the vast cost of inadequately treated chronic pain, whether measured in terms of human suffering and degraded quality of life or in terms of the literal costs of health care and lost productivity ($600 billion/year). Ideas about the potential value of alternative non-pharmacologic therapies have flourished despite the lack of comparative effectiveness studies. Absolute proscription of co-prescription of opioids and benzodiazepines appears to have effectively become the law of the land, even as studies supporting this concept have yielded data that are at best suggestive. These studies have also revealed the complexity of this issue. The relative effectiveness and risks of alternatives to benzodiazepines for treatment of idiopathic insomnia and anxiety have received no consideration. The potential role of depression in contributing to the adverse effects of chronic pain and its treatment and the potential value of aggressive treatment of depression in chronic pain patients have scarcely been considered.

The causes of the opioid crisis are now coming to light and a coherent narrative can be constructed. It seems that the CDC, in attempting to deal with a crisis in the streets by restricting treatment of pain in clinics, has created a second very serious crisis, this one involving 18 million patients in moderate to severe chronic pain. These CDC efforts have not addressed the crisis in the streets, one now accounting for nearly 3/4 of opioid deaths (109). This is a crisis of community economic failure, poverty, social isolation, hopelessness, and serious mental health problems.

Clearly it is time to return to the scientific evidence bearing on these issues, of which there is a considerable body. We now have a fairly clear picture of what needs further study. Innovative RCT designs have been proposed, e.g., EERGW, to test opioid efficacy and dosage variability, to conduct comparative effectiveness studies, and to assess the impact of comorbidities such as depression. Much is known about how to treat opioid addiction. What is lacking is adequate funding and implementation of treatment programs. Management of chronic pain is complex, labor intensive, requires considerable investment of health care resources, and entails significant risk. Major improvements in training of physicians (45), health care infrastructure, and re-imbursement policies are needed to optimize care and minimize risk.

## AUTHOR CONTRIBUTIONS

SN researched and wrote the manuscript. Much of the manuscript reflects an ongoing scientific dialogue between SN and RL over the course of 3 years. RL reviewed and critiqued the manuscript. JW was responsible for the statistical analyses. All authors have reviewed the manuscript and concur in its content.

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Practical Pain Management



Opioids

# Commentary: How to Fill the Holes in the CDC Opioid Prescribing Guideline Revisions

The authors propose revisions to the CDC's 12 draft guideline updates as well as two additional recommendations on managing depression in patients with chronic pain and protecting healthcare professionals trying to treat pain.

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**Feb 16, 2022**
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## A Commentary

On July 16, 2021, the Board of Scientific Counselors (BSC)of the CDC National Center for Injury Prevention and Control (NCIPC) held a public meeting by podcast. The agenda for this meeting was three-fold:

1. To review the process and progress in an ongoing revision of the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain
2. To review findings of the advisory CDC Opioid Workgroup (OWG) appointed by the BSC in January 2020; the OWG was tasked with overseeing and evaluating an interim draft of the revised CDC guideline generated by the NCIPC writers group.

③ To hear public comment on the 2016 guideline and its interim revision

The meeting minutes have been released and are available, and a full revision to the controversial CDC guideline is expected in 2022.

The OWG review of draft revisions to the CDC guideline was structured around a top-level listing of 12 recommendations made by the NCIPC writers group with observations and concerns voiced by members of the OWG. The report was phrased to preserve the anonymity of its contributors. Several central issues[1] stand out, paraphrased from a report by the OWG Chair:

- The draft rewrite lacks balance in its treatment of public health concerns versus individual patient quality of life. It fails to adequately address the benefits of prescription opioids in comparison to their perceived risks.
- The draft rewrite omits mention of key references while relying on a large number of studies in which a single individual is a principal author.
- The draft guideline could be used to force tapers on legacy patients.
- A lack of research support for the recommended 50/90 MMED dose thresholds or 3-7 day prescription limitations.
- The draft rewrite may facilitate further "misinterpretation" and "misuse" of the original 2016 guideline.

Many of the concerns raised by the BSC OWG are similar to those expressed in June 2020 by the American Medical Association,[2] and by people living with chronic pain during the public comment session of the July 2021 meeting and earlier BSC meetings.

It should be noted that regulating the practice of medicine in general and of opioid prescribing practices in particular, is strongly at odds with the overall CDC mission and might reasonably be considered to represent substantial overreach. This being the case, some might argue that the only CDC action consistent with its mission would be to withdraw entirely from any and all attempts to regulate pain management by clinicians and to withdraw and repudiate the 2016 CDC guidelines. On the other hand, the illicit opioid crisis, which now accounts for more than three-fourths of opioid-associated deaths,[3] arguably *does* fall within the CDC mission.W

We believe that if the CDC is allowed to continue along a pathway so at odds with its overall mission and scope of practice, then a major change of direction and emphasis is needed in the ongoing revision of the 2016 guideline. The following proposed revisions represent an attempt by the authors (Lawhern/Nadeau) to outline key corrections.

The "draft recommendation" quotations below from the July 2021 revision draft are verbatim from the BSC OWG report.[1] All Category A references (defined as mandatory rather than advisory for all clinicians) have been removed. Evaluation of Evidence Types should properly be performed by other medical specialists, rather than by the authors of this paper.

Our (Drs. Lawhern & Nadeau) proposals follow.

## Acute Pain

**July 2021 CDC OWG Draft Recommendation #1:** "Nonopioid therapies are preferred for many common types of acute pain. Clinicians should consider opioid therapy for acute pain only if benefits are anticipated to outweigh risks to the patient." (Recommendation Category: A; Evidence Type: 3)

**Lawhern/Nadeau Proposed Revision #1:** Pain is the symptom that most often brings people to a doctor's office. Every patient is an individual. Due to individual variations in treatment effectiveness and side effects, there is no one-size-fits-all patient or treatment plan.[4] Every treatment plan must reflect a cooperative and collaborative relationship of trust between the patient and one or more medical professional(s), integrating findings from in-person examination, medical history, diagnostic tests, patient reports, and patient response to treatment.

Non-opioid therapies may be preferred for many common types of acute pain of low to moderate intensity. Acknowledging public concerns on risks of opioids, opioid therapies and multimodal treatments nonetheless presently play indispensable roles in treating moderate to severe pain.

The medical literature lacks evidence for the validity of mandated limits on opioid dose (MMED).[1] In fact, the literature provides considerable evidence of a 15-fold variability in opioid dose requirements, related to severity of pain, genetic differences in metabolism of drugs and prodrugs, and poorly understood differences in central nervous system sensitivity to opioids.[5]

## Subacute and Chronic Pain

**July 2021 CDC OWG Draft Recommendation #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 known risks and realistic benefits of opioid therapy, should establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. If

opioids are used, they should be combined with other therapies as appropriate." (Recommendation Category: A, Evidence Type: 3)

**Lawhern/Nadeau Proposed Revision #2:** Nonopioid, non-invasive, and nonpharmacological therapies might help some patients, some of the time, for both subacute and chronic pain. However, there are presently no published randomized double-blind trials that directly compare opioid therapy to non-opioid pharmacological therapy or to nonpharmacological therapy on an either/or basis.[6,7] There are furthermore no studies testing whether non-opioid pharmacological therapies or nonpharmacological therapies can serve a useful purpose as adjuvant treatments that might enable opioid dose reduction. Thus, nonopioid therapies, pharmacological or nonpharmacological, cannot be said to be "preferred" to opioid therapies in the complete absence of supportive scientific evidence. A significant investment in rigorously conducted trials is needed to establish the most effective roles of non-opioid therapies in medical practice.

Before starting opioid therapy for chronic pain, clinicians should discuss with patients known risks and realistic benefits; establish treatment goals for pain, function, and management of side effects; and establish a plan for how opioid therapy will be reduced or discontinued in the event that underlying medical conditions resolve.

## Immediate-Release and Extended-Release Opioids

**July 2021 CDC OWG Draft Recommendation #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 and Evidence Type: 3)

**Lawhern/Nadeau Proposed Revision #3:** In managing acute, subacute, or chronic pain, clinicians should tailor opioid medications as necessary to address both continuous and "breakthrough" pain, and to manage side effects. Long-acting opioids have the advantage of providing sustained relief of pain over extended periods of time. Because they are to be taken at specified times of the day, the risk of overdose (because doses were taken too close together) is minimized. However, they require very careful dose titration as it takes a substantial amount of time for drug levels to achieve steady state. The possibility of a clinically significant incidence of tolerance cannot be excluded. Short-acting opioids have an advantage in treating acute flares of pain but may be susceptible to inadvertent double dosing, hence overdose. Thus, careful patient monitoring and education are essential, particularly in the initial stages of assessing therapy outcomes, whenever dose level is increased, or when opioid medications are changed.

## Opioid-Naïve Patients

**July 2021 CDC OWG Draft Recommendation #4:** "When opioids are started for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to > 90 MME/day." (Category A, Evidence type 3)

**Lawhern/Nadeau Proposed Revision #4:** When opioids are started for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage and titrate very gradually to dosage sufficient to achieve adequate control of pain without causing cognitive or neurologic side effects. Individualization of treatment is of cardinal importance. If opioids are continued or increased for subacute or chronic pain, clinicians should carefully reassess evidence of individual benefits and risks and monitor outcomes to ensure that patients are not over-medicated. Common side effects such as nausea and constipation can be managed in many patients. Cognitive or neurological impairment, sedation, or impairment in ability to perform customary activities (including work) should be viewed as evidence of excessive dosage or the need to switch to an alternative opioid. The estimated risk of opioid-associated death rises more or less linearly from 0.25%/year for dosage of ≥100 MME/day, to 0.5%/year for dosage >400 MMED, without an inflection point.[5] Because risks of this level are unlikely to be of major concern to most patients, and because there is a well-established 15-fold variability in opioid dose requirements, there is no scientific basis for prioritizing 50 MME/day or 90 MME/day.[5]

## Legacy Patients on Opioids

**July 2021 CDC OWG Draft Recommendation #5:** "For patients already receiving higher opioid dosages (eg, >90 MME/day), clinicians should carefully weigh benefits and risks and exercise care when reducing or continuing opioid dosage. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids." (Recommendation Category: A and Evidence Type: 4)

**Lawhern/Nadeau Proposed Revision #5:** In the absence of substantial evidence of patient non-compliance with opioid therapy plans, sustained over multiple visits, no patient should be involuntarily tapered or denied pain treatment solely on the basis of their present dosage level. For patients with a documented history of inappropriate opioid use (dosing by inappropriate routes; admissions for overdose demonstrably related to opioid overdose – reflected in response to administration of an opioid receptor blocker, eg, Naloxone; repeated reports of accidental loss of medication or premature requests for refills; and doctor shopping), more frequent monitoring of treatment outcomes may be warranted. Persistent patient non-compliance should be reason for a timely patient-physician conference.

Opioid tapering is associated with increased incidence of mental health crises and mortality among patients prescribed opioids long-term for chronic conditions.[8] For patients who wish to reduce their opioid dosage with the assistance of medical providers, gradual tapering should be initiated according to published HHS guidelines to assure safety and comfort during the taper.[9] There should be frequent physician monitoring of pain outcomes and withdrawal symptoms.

Development of opioid tolerance over time in some chronic pain patients is an accepted phenomenon. It may be confused with "pseudo-addiction."[10,11] Scientific evidence for what has been called "opioid induced hyperalgesia" is at best equivocal.[12]

## The 3-7 Day Prescription Limit

**July 2021 CDC OWG Draft Recommendation #6:** "When opioids are used for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. One to three days or less will often be sufficient; more than seven days will rarely be needed." (Recommendation Category: A and Evidence Type: 4)

**Lawhern/Nadeau Proposed Revision #6:** When opioids are used for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. At present, there is no medical evidence supporting any default period of treatment that applies generally.[1] Acute care patients should be monitored on a daily basis to determine who may have been under-medicated or over-medicated, or in whom an acute pain syndrome may have begun to evolve into a chronic pain syndrome.

Ongoing research is needed to more fully characterize the range of patient responses to acute pain care in terms of adequacy of pain control, quality of life, and patient satisfaction.

## Ongoing Opioid Therapy

**July 2021 CDC OWG Draft Recommendation #7:** "Clinicians should continue opioid therapy for subacute or chronic pain only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety. Clinicians should evaluate benefits and harms 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 harms of continued therapy with patients every 3 months or more frequently." (Recommendation Category: A, Evidence Type: 4)

**Lawhern/Nadeau Proposed Revision #7:** Clinicians should continue opioid therapy for subacute or chronic pain if there has been no resolution of underlying medical disorders or conditions, or when there is clinically meaningful improvement in pain and/or function over conditions that prevailed at initiation of therapy. Clinicians should evaluate benefits and side effects and

patients should be clinically evaluated (in person or via telemedicine) whenever dose escalation is contemplated.

Monitoring of ongoing patient outcomes should occur on a schedule established by the clinician based on medical conditions and the patient's response to treatment. Monitoring may be accomplished by telemedicine interviews for patients living in rural or remote areas, or who have transportation challenges.

## Opioid Risks, Overdose, and Related Harms

**July 2021 CDC OWG Draft Recommendation #8:** "Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss with patients. Clinicians should incorporate into the management plan, strategies to mitigate risk, including offering Naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present." (Recommendation Category: A, Evidence Type: 4)

**Lawhern/Nadeau Proposed Revision #8:** Factors associated with overdoses of prescribed opioids have not received adequate scientific attention. They likely include excessively rapid dosage titration by physicians, inadvertent double dosing by patients, insufficiently close clinical monitoring, and dosage escalation outside the context of clinic visits.[5] Clinical warning signs, including reports by family members of altered mentation, and observation of cognitive or neurological impairment by clinicians, should lead to immediate measures to improve discipline in opioid dosing or reduction in total dosage.

Whereas opioid receptor antagonists have proven to be of value in mitigation of overdoses in those using illicit opioids, there is no scientific evidence of their value in clinical populations. Prescription of antagonists should not be considered a substitute for prudent clinical care.

There is now solid clinical evidence that concurrent use of benzodiazepines and opioids is associated with an approximate doubling of risk of death.[13,14] However, it is uncertain whether this increased risk is related to co-prescription per se, or instead to the combination of underlying morbidities, eg, pain plus anxiety or insomnia. Drugs with well-demonstrated adverse effects, eg, hydroxyzine and quetiapine, are presently being used inappropriately simply because they are not benzodiazepines.

Whenever benzodiazepines and opioids are co-prescribed, the patient and their co-resident family should be fully informed of the reasons for this program of treatment and the possible risks thereof.

## Drug Monitoring

**July 2021 CDC OWG Draft Recommendation #9:** "Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for acute or chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months." (Recommendation Category: A, Evidence Type: 4)

**Lawhern/Nadeau Proposed Revision #9:** Clinicians should review the patient's recent history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is also receiving opioids from other physicians (doctor shopping). Clinicians should review PDMP data when starting opioid therapy for acute or chronic pain and in the event of persistent indications of patient non-compliance with opioid therapy. However, clinicians should also be aware that PDMP data may include errors. No patient should be discharged solely because of anomalies reported in a PDMP. Rather, these anomalies should prompt a serious conversation with the patient. Legislated mandatory periodic reviews of PDMP records may impose workload on clinicians without contributing to positive patient outcomes.[15]

**July 2021 CDC OWG Draft Recommendation #10:** "When prescribing opioids for chronic pain, clinicians should use drug testing before starting opioid therapy and consider drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs." (Recommendation Category: B, Evidence Type: 4)

**Lawhern/Nadeau Proposed Revision #10:** We feel there is insufficient scientific evidence that urine drug testing is of value in pain management. Urine drug testing sends a strong message to patients that they are not to be trusted — potentially seriously undermining the relationship of mutual trust between patient and physician that should be the foundation of pain management.

## Benzodiazepines and Opioid Use Disorder: Drug-Drug Interactions

**July 2021 CDC OWG Draft Recommendation #11:** "Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants." (Recommendation Category: A, Evidence Type: 3)

**Lawhern/Nadeau Proposed Revision #11:** Clinicians should exercise caution in the co-prescription of opioids and benzodiazepines. The estimated annual opioid associated risk of death is 0.25% for regimens of greater than 100 MMED and gradually rises (without an inflection point) to 0.5% for regimens of >400 MMED.[5] The co-prescription of benzodiazepines roughly doubles this risk.[5] However, it is not known to what extent this reflects the combined effects of the drugs or the combined effect of comorbidities (e.g., pain and generalized anxiety or insomnia). Benzodiazepines are effective in treating generalized anxiety disorder and insomnia and may provide some pain relief through their muscle relaxant effects. Hydroxyzine is often substituted for benzodiazepines for treatment of anxiety but is a drug with potent anticholinergic effects, hence associated with degradation of memory formation and consolidation.[16] Quetiapine, often used as a substitute for benzodiazepines to treat insomnia, is an atypical neuroleptic, a drug class associated with a doubling of risk of mortality.[17]

**July 2021 CDC OWG Draft Recommendation #12:** "Clinicians should offer or arrange treatment with medication for patients with opioid use disorder." (Recommendation Category: A, Evidence Type: 2)

**Lawhern/Nadeau Proposed Revision #12:** Opioid use disorder (OUD) is likely rare in clinical patients.[5,18] The diagnosis of OUD in the clinical population is probably most often prompted by requests for higher dosage in the context of inadequately controlled pain ("pseudo-addiction"),[10,11] clinician failure to recognize that acute pain has evolved into chronic pain, or by patient difficulty in maintaining adequate discipline in their use of opioids. When there is compelling evidence of OUD, patients should be referred to clinicians trained and certified in the treatment of OUD, in addition to continuing coordinated pain therapy.

## Additional Recommendations From the Authors

**Lawhern/Nadeau Proposed Addition #13:** The prevalence of concurrent chronic pain and depression and the synergistic effect of the two disorders on suffering should be recognized.[5,19] Vigorous efforts should be made to ascertain the existence of depression and vigorous treatment of depression should be consistently pursued, either by primary care physicians, pain specialists, or psychiatrists to whom these patients are referred.

**Lawhern/Nadeau Proposed Addition #14:** The AMA has publicly stated that the 2016 CDC guideline on prescribing opioids for chronic pain has harmed numerous patients.[2] As an example, MMED thresholds declared in the 2016 guideline as a reason for review of medical risks and benefits have been misapplied as hard limitations on therapy available to individuals in multiple US states,[20] and as criteria for legal or professional sanctions against doctors who prescribe doses higher than 90 MMED. To correct this damage and support patient access to safe and effective opioid therapy, the authors believe that an additional CDC recommendation needs to be directed to state medical boards, the US Department of Justice, and the US Drug Enforcement Agency. The language may be written along these lines:

CDC guidelines must be viewed as strictly advisory in nature. Recommendations are not mandatory best practices and do not establish a standard of care or proof of legitimate medical purpose, and should not be misinterpreted or misused as such. The CDC joins the American Medical Association and multiple other professional associations and academies in calling for repeal of all state legislation mandating arbitrary limits on opioid dose or duration.[2]

These revised recommendations should not be used as a basis for sanctions, prosecution, or other legal or administrative action against medical professionals (doctors, physician assistants, nurse practitioners, pharmacists, or others trained and licensed to prescribe or dispense medications scheduled by the US Drug Enforcement Agency).

*Observations and recommendations offered in this paper by the authors do not represent the views of the US Department of Veterans Affairs or the University of Florida College of Medicine.*

***Editor's Note*: the opioid prescribing guideline revision has been released and is open for public comment thorugh April 11, 2022.**

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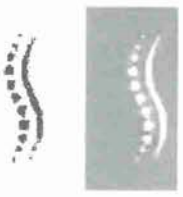
**Spinal Cord Stimulation as a Treatment for Refractory Painful Diabetic Neuropathy**

Jijun Xu, MD, PhD



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Don L. Goldenberg, MD

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Christine Rhodes, MS

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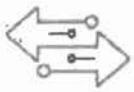

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Kathryn A. Witzeman, MD, FACOG

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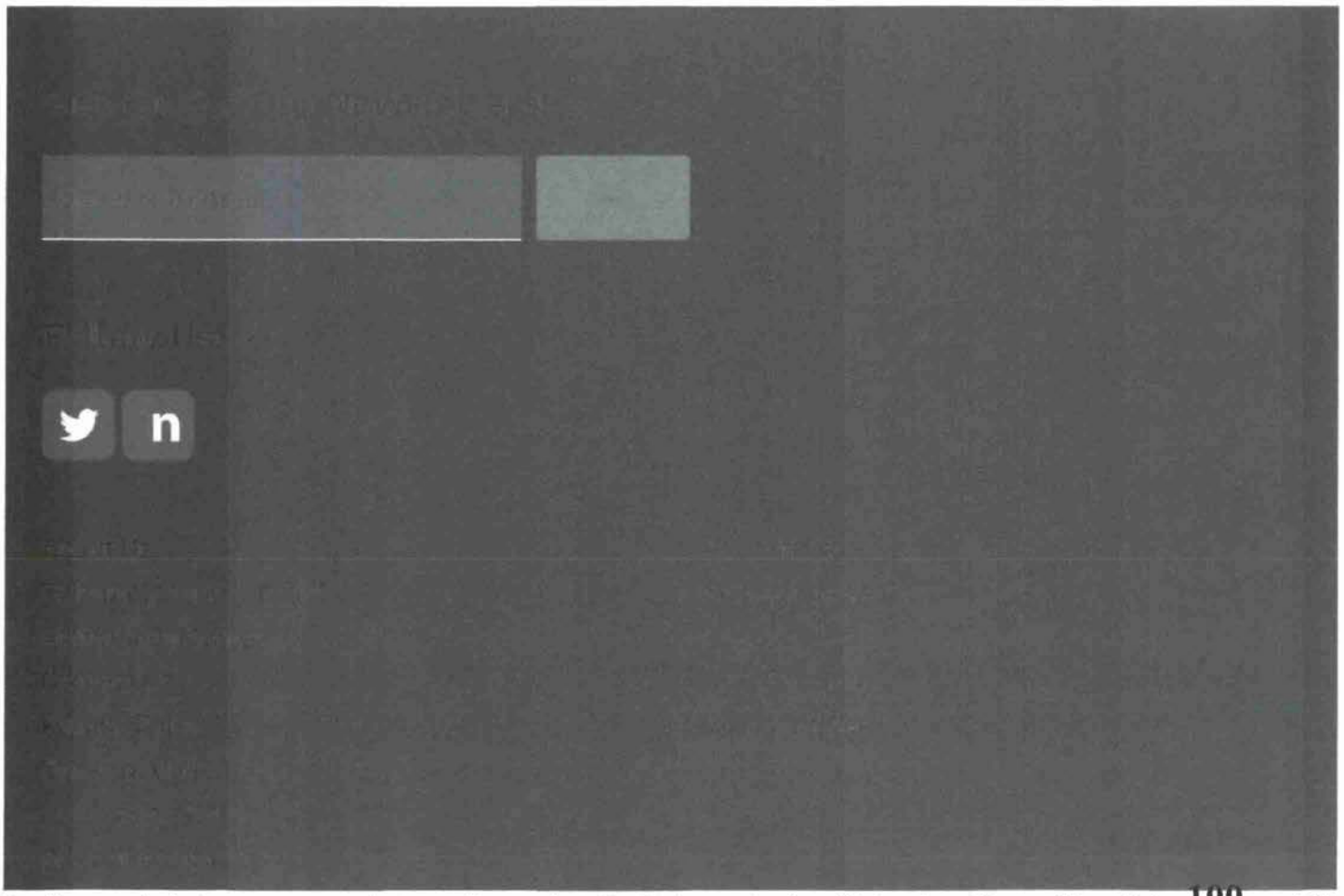


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**Morton, Colanthia D. (DHP)**

**Subject:** FW: Finally, Mainstream Media Are Beginning to Get the Message!

**From:** Richard Lawhern <lawhern@hotmail.com>
**Sent:** Tuesday, March 14, 2023 9:57 AM
**To:** NCIPCBSC (CDC) <ncipcbsc@cdc.gov>; CDCExecSec (CDC) <cdcexecsec@cdc.gov>; Patricia McSorley <patricia.mcsorley@azmd.gov>; Vince Culotta <vculotta@lsbme.la.gov>; Shirley (NIH/NIDA) [E] Simson <simsons@nida.nih.gov>; Sharon Hertz MD <sharon.hertz@fda.hhs.gov>; Alicia (HHS/OASH) Scott <alicia.richmond@hhs.gov>; Cecilia Spitznas <cecelia_m_spitznas@ondcp.eop.gov>; Diana Perez-Rivera <diana.perez-rivera@cms.hhs.gov>; Friedholm Sandbrink <friedhelm.sandbrink@va.gov>; hilda schulke <hilda.schulke@nih.gov>; John Driscoll <john.driscoll@mail.house.gov>; Compton, Kimberly <kimberly.compton@fda.hhs.gov>; Linda Porter <porterl@ninds.nih.gov>; Hurt, Nikki (Markey) <nikki_hurt@markey.senate.gov>; Nora Volkow <nvolkow@nida.nih.gov>; HHS Assistant Secretary for Planning & Eval <epaedeareport@hhs.gov>; Sondra Adkinson <sondra.adkinson@va.gov>; ONDCP <cspitznas@ondcp.eop.gov>; Wells, Theresa * <theresa.wells@fda.hhs.gov>; Harp, William L. (DHP) <William.Harp@DHP.VIRGINIA.GOV>
**Subject:** Finally, Mainstream Media Are Beginning to Get the Message!

From yesterday on CBS News, reporting by Sam Whitehead and Andy Miller, Kaiser Health News

# CDC's new opioid guidelines are too little, too late for chronic pain patients, experts say

Credit for discovery to my colleague Larry Aubry

https://www.nbcnews.com/health/health-news/cdcs-new-opioid-guidelines-little-late-chronic-pain-patients-rcna74248

CDC softens guidelines for doctors who prescribe opioids

In November, the agency eased the guidelines for prescribing opioids for pain, allowing physicians more flexibility.

www.nbcnews.com

So far, none of those who commented for the Kaiser Health News reporting were quite willing to face the music and tell the whole truth: rates of opioid prescribing are unrelated to rates of either hospitalizations for opioid toxicity, or drug-overdose-related mortalities. And despite CDC claims to the contrary, they have been unrelated for at least 12 years.

Richard A "Red" Lawhern PhD

Patient Advocate

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Facebook: https://www.facebook.com/red.lawhern

My Publications: http://www.face-facts.org/Lawhern
Personal Website: http://www.lawhern.org

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— People like Rheba Smith, of Atlanta, say they have struggled to get opioid prescriptions written and filled the past few years. Guidelines from the Centers for Disease Control and Prevention in 2016 inspired laws cracking down on opioid prescribing practices. Andy Miller / KHN

SAVE

March 13, 2023, 9:55 AM EDT / Source: Kaiser Health News

**By Sam Whitehead, Kaiser Health News and Andy Miller, Kaiser Health News**

Jessica Layman estimates she has called more than 150 doctors in the past few years in her search for someone to prescribe opioids for her chronic pain.

"A lot of them are straight-up insulting," said the 40-year-old, who lives in Dallas. "They say things like 'We don't treat drug addicts.'"

Layman has tried a host of non-opioid treatments to help with the intense daily pain caused by double scoliosis, a collapsed spinal disc, and facet joint arthritis. But she said nothing worked as well as methadone, an opioid she has taken since 2013.

The latest phone calls came late last year, after her previous doctor shuttered his pain medicine practice, she said. She hopes her current doctor won't do the same. "If something should happen to him, there's nowhere for me to go," she said.

Layman is one of the millions in the U.S. living with chronic pain. Many have struggled to get opioid prescriptions written and filled since 2016 guidelines from the Centers for Disease Control and Prevention inspired laws cracking down on doctor and pharmacy practices. The CDC recently updated those recommendations to try to ease their impact, but doctors, patients, researchers, and advocates say the damage is done.

"We had a massive opioid problem that needed to be rectified," said Antonio Ciaccia, president of 3 Axis Advisors, a consulting firm that analyzes prescription drug pricing. "But the federal crackdowns and guidelines have created collateral damage: patients left high and dry."

Born of an effort to fight the nation's overdose crisis, the guidance led to legal restrictions on doctors' ability to prescribe painkillers. The recommendations left many patients grappling with the mental and physical health consequences of rapid dose tapering or abruptly stopping medication they'd been taking for years, which carries risks of withdrawal, depression, anxiety, and even suicide.

## Help for people with chronic pain

In November, the agency released new guidelines, encouraging physicians to focus on the individual needs of patients. While the guidelines still say opioids should not be the go-to option for pain, they ease recommendations about dose limits, which were widely viewed as hard rules in the CDC's 2016 guidance. The new standards also warn doctors about risks associated with rapid dose changes after long-term use.

But some doctors worry the new recommendations will take a long time to make a meaningful change – and may be too little, too late for some patients. The reasons include a lack of coordination from other federal agencies, fear of legal consequences among providers, state policymakers hesitant to tweak laws, and widespread stigma surrounding opioid medication.

The 2016 guidelines for prescribing opioids to people with chronic pain filled a vacuum for state officials searching for solutions to the overdose crisis, said Dr. Pooja Lagisetty, an assistant professor of medicine at the University of Michigan Medical School.

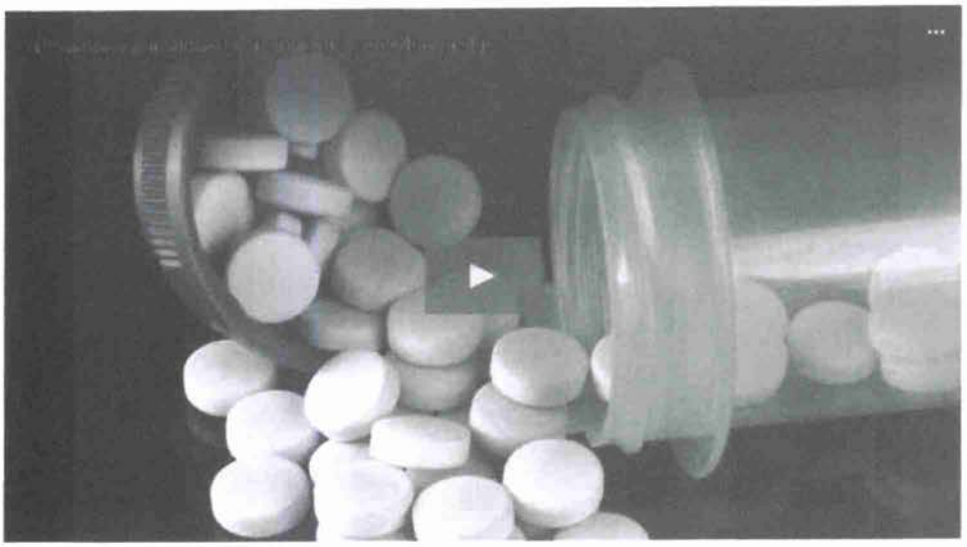
The dozens of laws that states passed limiting how providers prescribe or dispense those medications, she said, had an effect: a decline in opioid prescriptions even as overdoses continued to climb.

The first CDC guidelines "put everybody on notice," said Dr. Bobby Mukkamala, chair of the American Medical Association's Substance Use and Pain Care Task Force. Physicians reduced the number of opioid pills they prescribe after surgeries, he said. The 2022 revisions are "a dramatic change," he said.

The human toll of the opioid crisis is hard to overstate. Opioid overdose deaths have risen steadily in the U.S. in the past two decades, with a spike early in the covid-19 pandemic. The CDC says illicit fentanyl has fueled a recent surge in overdose deaths.

Taking into account the perspective of chronic pain patients, the latest recommendations try to scale back some of the harms to people who had benefited from opioids but were cut off, said Dr. Jeanmarie Perrone, director of the Penn Medicine Center for Addiction Medicine and Policy.

"I hope we just continue to spread caution without spreading too much fear about never using opioids," said Perrone, who helped craft the CDC's latest recommendations.



Christopher Jones, director of the CDC's National Center for Injury Prevention and Control, said the updated recommendations are not a regulatory mandate but only a tool to help doctors "make informed, person-centered decisions related to pain care."

Multiple studies question whether opioids are the most effective way to treat chronic pain in the long term. But drug tapering is associated with deaths from overdose and suicide, with risk increasing the longer a person had been taking opioids, according to research by Dr. Stefan Kertesz, a professor of medicine at the University of Alabama-Birmingham.

He said the new CDC guidance reflects "an extraordinary amount of input" from chronic pain patients and their doctors but doubts it will have much of an impact if the FDA and the Drug Enforcement Administration don't change how they enforce federal laws.

**Recommended**

U.S. NEWS

**U.S. sues Rite Aid for missing opioid red flags**

HEALTH NEWS

**Following Eli Lilly, drugmaker Novo Nordisk announces cuts to insulin prices**

The FDA approves new drugs and their reformulations, but the guidance it provides for how to start or wean patients could urge clinicians to do so with caution, Kertesz said. The DEA, which investigates physicians suspected of illegally prescribing opioids, declined to comment.

The DEA's pursuit of doctors put Danny Elliott of Warner Robins, Georgia, in a horrible predicament, said his brother, Jim.

In 1991, Danny, a pharmaceutical company rep, suffered an electric shock. He took pain medicine for the resulting brain injury for years until his doctor faced federal charges of illegally dispensing prescription opioids, Jim said.

Danny turned to doctors out of state – first in Texas and then in California. But Danny's latest physician had his license suspended by the DEA last year, and he couldn't find a new doctor who would prescribe those medications, Jim said.

Danny, 61, and his wife, Gretchen, 59, died by suicide in November. "I'm really frustrated and angry about pain patients being cut off," Jim said.

Danny became an advocate against forced drug tapering before he died. Chronic pain patients who spoke with KHN pointed to his plight in calling for more access to opioid medications.

Even for people with prescriptions, it's not always easy to get the drugs they need.

Pharmacy chains and drug wholesalers have settled lawsuits for billions of dollars over their alleged role in the opioid crisis. Some pharmacies have seen their opioid allocations limited or cut off, noted Ciaccia, with 3 Axis Advisors.

Rheba Smith, 61, of Atlanta, said that in December her pharmacy stopped filling her prescriptions for Percocet and MS Contin. She had taken those opioid medications for years to manage chronic pain after her iliac nerve was mistakenly cut during surgery, she said.

— Rheba Smith, of Atlanta, has struggled to get a pharmacy to fill her opioid prescriptions. Many have found it harder to get opioid prescriptions written and filled since 2016 CDC guidelines inspired laws cracking down on doctor and pharmacy practices. Andy Miller / KHN

Smith said she visited nearly two dozen pharmacies in early January but could not find one that would fill her prescriptions. She finally found a local mail-order pharmacy that filled a one-month supply of Percocet. But now that drug, along with MS Contin, are not available, the pharmacy told her.

"It has been a horrible three months. I have been in terrible pain," Smith said.

Many patients fear a future of constant pain. Layman thinks about the lengths she'd go to in order to get medication.

"Would you be willing to buy drugs off the street? Would you be willing to go to an addiction clinic and try to get pain treatment there? What are you willing to do to stay alive?" she said. "That is what it comes down to."

———Sam Whitehead, Kaiser Health News

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RESEARCH, PRESS RELEASES | AUGUST 4, 2022

# Almost 90 Percent of People with Opioid Use Disorder Not Receiving Lifesaving Medication

Researchers Sound Alarm on Treatment Gap & Suggest Ways to Remove Treatment Barriers as Opioid Overdoses Soar to Historic Levels

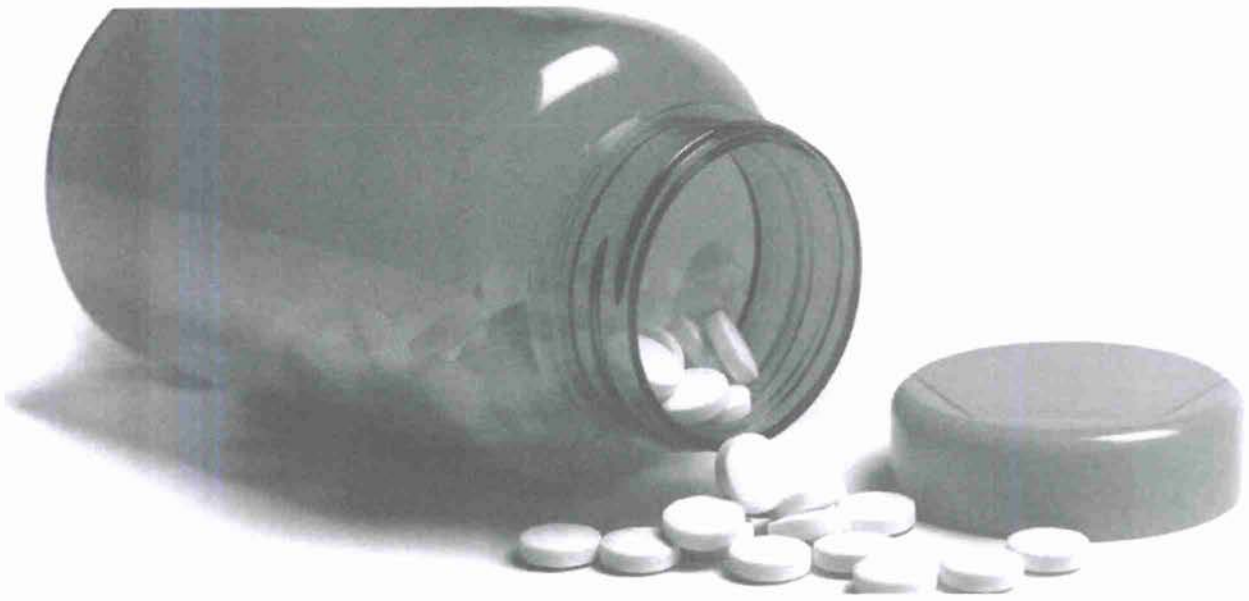

PHOTO: PETER ARNOLD/GETTY

The opioid overdose and death epidemic continues to worsen across the United States, but medications such as methadone, buprenorphine, and extended-release

naltrexone are proven to reduce opioid overdoses by more than 50 percent. New findings led by researchers at NYU Grossman School of Medicine indicate the vast majority, or 86.6 percent, of people living with opioid use disorder (OUD) are not receiving these evidence-based, lifesaving medications.

Published online August 4 in the *International Journal of Drug Policy*, the study examined the gap between new estimates of OUD prevalence and the use of medications for OUD (MOUD) at the national and state levels from 2010 through 2019. Although the use of MOUD has grown by more than 100 percent over the last decade, this rise in treatment has failed to keep pace with OUD and skyrocketing overdose mortality rates—largely driven by fentanyl, a potent synthetic opioid up to 50 times stronger than heroin.

A recent report from the Centers for Disease Control and Prevention revealed opioid overdose deaths climbed 30 percent during the first year of the COVID-19 pandemic nationally, with Black, American Indian, and Alaska Native populations bearing disproportionate shares of the increase.

"Our findings highlight the urgency of removing barriers to accessing medications to treat opioid use disorder, while expanding the availability of these medications," says Noa Krawczyk, PhD, an assistant professor in the Department of Population Health, a member of the Center for Opioid Epidemiology and Policy at NYU Langone, and lead author of the study. "But what we have is way beyond a simple treatment capacity problem. We need to rethink how treatment for opioid use disorder is delivered, eliminate stigma, make it easier for people to enter and remain in treatment, as well as ensure that all treatment programs provide and encourage use of evidence-based medications that we know save lives."

According to Dr. Krawczyk, more than 70 percent of residential treatment programs across the country do not offer MOUD. Other ways to expand access to MOUD could include removing special waiver requirements so that more physicians can prescribe buprenorphine, as well as expanding the deployment of MOUD by mobile health clinics and community-based organizations, and within the criminal justice system. Making methadone

less controlled and more accessible through avenues other than highly regulated opioid treatment programs is also long overdue, says Dr. Krawczyk.

## How the Study Was Conducted

To determine the gap between people with OUD and the number of people receiving MOUD, the investigators analyzed two different sources: a publicly available database that tracks the dispensing of MOUD by licensed methadone clinics and a private database of outpatient pharmacy claims that tracks prescriptions filled for buprenorphine and extended-release naltrexone (MOUD that can be prescribed from a doctor's office). The researchers then calculated the percent change in national and state-specific rates of persons receiving MOUD over the past year (2018 to 2019) and past decade (2010 to 2019), using rates per 100,000 people. Their analysis revealed the following findings:

- There was a 105.6 percent increase in the rate of MOUD receipt across the United States from 2010 to 2019.
- As of 2019, 86.6 percent of people with OUD were not receiving MOUD.
- State-specific findings indicate a wide variation in past-year OUD prevalence and MOUD treatment gaps.
- MOUD treatment rates were lowest in South Dakota (66.1 per 100,000) and highest in Vermont (1,342.6 per 100,000).
- As of 2019, the largest treatment gaps were in Iowa (97.3 percent), North Dakota (96.1 percent), and Washington, DC (95.1 percent).
- The smallest treatment gaps were in Connecticut (53.9 percent), Maryland (58.1 percent), and Rhode Island (58.6 percent).
- While all 50 states had increases in MOUD treatment rates, only Washington, DC, had a decrease of 9.2 percent between 2018 and 2019.

"Even in states with the smallest treatment gaps, at least 50 percent of people who could benefit from medications for opioid use disorder are still not receiving them," says Magdalena Cerdá, DrPH, a professor in the Department of Population Health, director of the

Center for Opioid Epidemiology and Policy, and the study's senior author. "We have a long way to go in reducing stigma surrounding treatment and in devising the types of policies and programs we need to ensure these medications reach the people who need them the most," says Dr. Cerdá.

In addition to Dr. Krawczyk and Dr. Cerdá, study co-authors from NYU Grossman School of Medicine are Bianca D. Rivera, MPH, CPH, and Victoria Jent, MPH. Additional co-authors are Katherine M. Keyes, PhD, MPH, from the Mailman School of Public Health, Columbia University; and Christopher M. Jones, PharmD, DrPH, MPH, from the National Center for Injury Prevention and Control, Centers for Disease Control and Prevention.

The study was supported by NYU Langone's Center for Opioid Epidemiology and Policy.

## Media Inquiries

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RESEARCH, TRANSLATIONAL MEDICINE, PRESS RELEASES

### Psychedelic Drug Therapy May Help Treat Alcohol Addiction

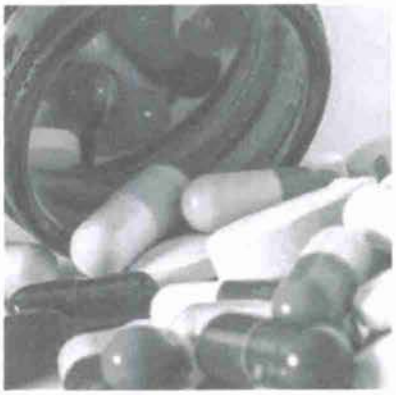
Together, psilocybin and psychotherapy reduced alcohol consumption by 83 percent among heavy drinkers.

August 24, 2022

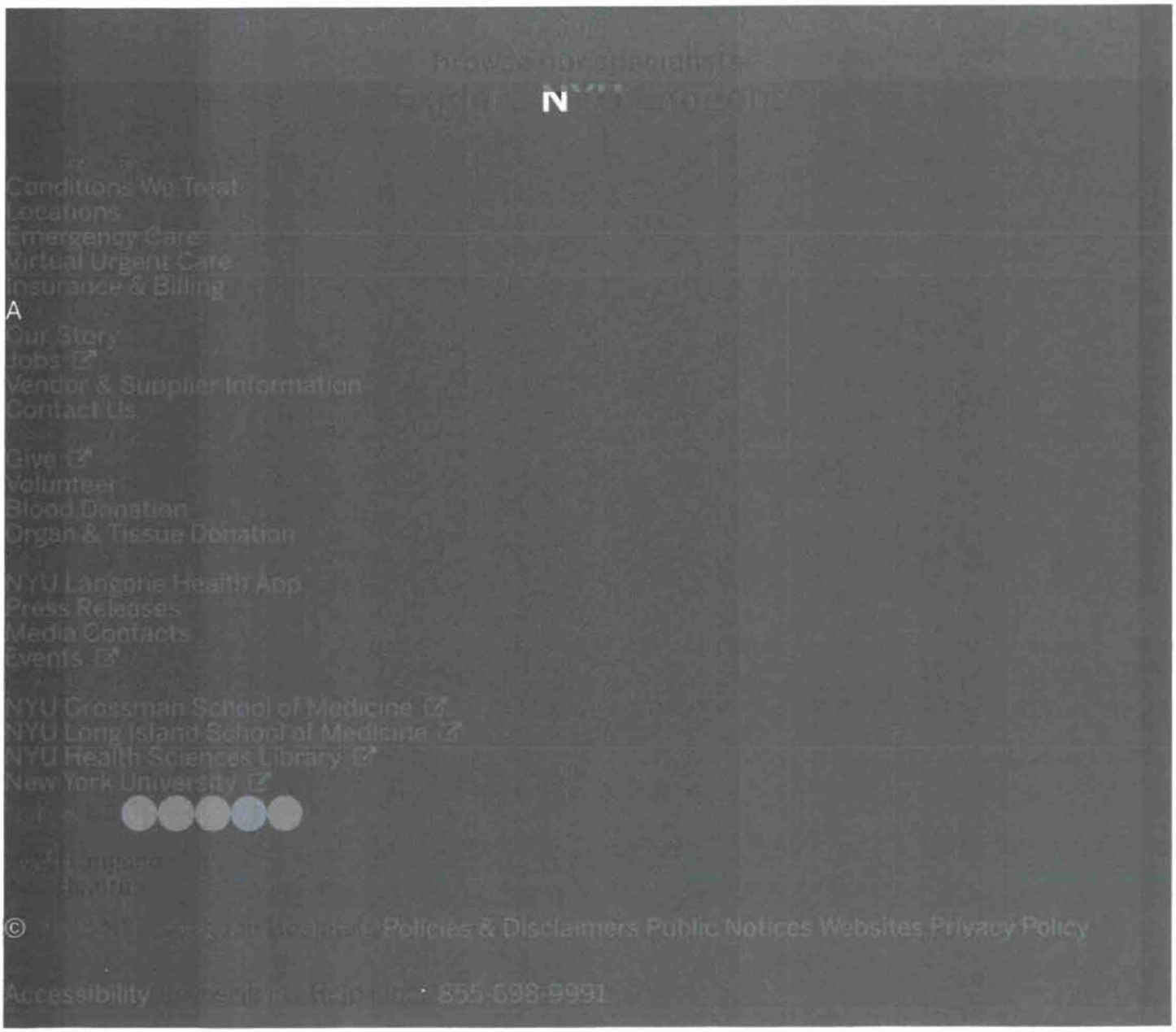
RESEARCH, PRESS RELEASES

# Overdose Deaths Caused by Opioids in Combination with Stimulants Hit Black Communities Hardest

Overdose deaths rose for Black people by more than three times the rate as non-Hispanic White people.



February 8, 2022



# Demystifying Buprenorphine Regulations for Pharmacists and Clinicians

Margaret Lowenstein, MD

Gilly Gehri, BA

Al Carter, MS, PharmD, RPh

Heidi Carroll, BS

Matthew Strait, MS

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# Disclosures

Our speakers, Dr. Margaret Lowenstein, Dr. Al Carter, Heidi Carroll, Matthew Strait, and Gilly Gehri declare that they do not have a current affiliation or financial arrangement with any ineligible companies that may have a direct interest in the subject matter of this continuing pharmacy education (CPE) activity within the past 24 months.

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All relevant financial relationships have been mitigated.

# Self Assessment Questions

1. Why is low-barrier care important?

2. As pharmacy workflow is streamlined, what proactive steps can pharmacists take to support this patient population?

3. How can I be a champion for low barrier MOUD access from the pharmacy level?

# Low-Barrier Buprenorphine Treatment

**Maggie Lowenstein, MD, MPhil, MSHP**

Penn Division of General Internal Medicine & Center for Addiction Medicine and Policy

# X-waiver is X-ed!

## Mainstreaming Addiction Treatment (MAT) Act Passed December 29, 2022

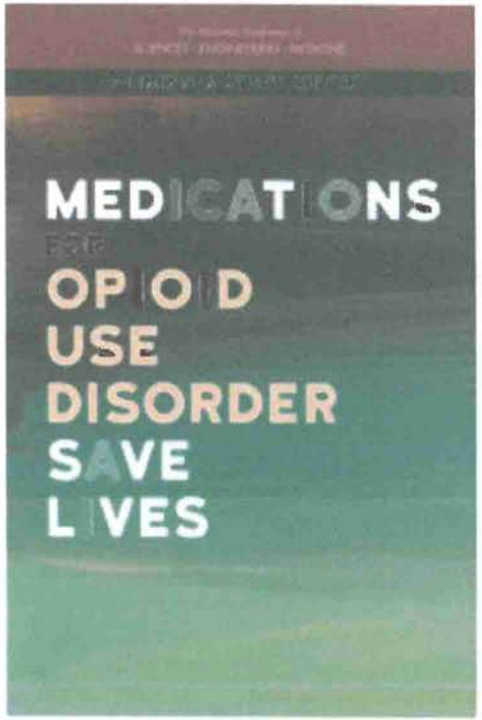
- **DATA-Waiver (X-waiver) no longer required to treat patients with buprenorphine for OUD**
- Buprenorphine prescriptions can be written with standard DEA number
- No limits or caps on patients for buprenorphine treatment.

# MOUDs Save Lives

Opioid agonist therapy reduces **all-cause** and **overdose** mortality by ~50%

**Also associated with...**

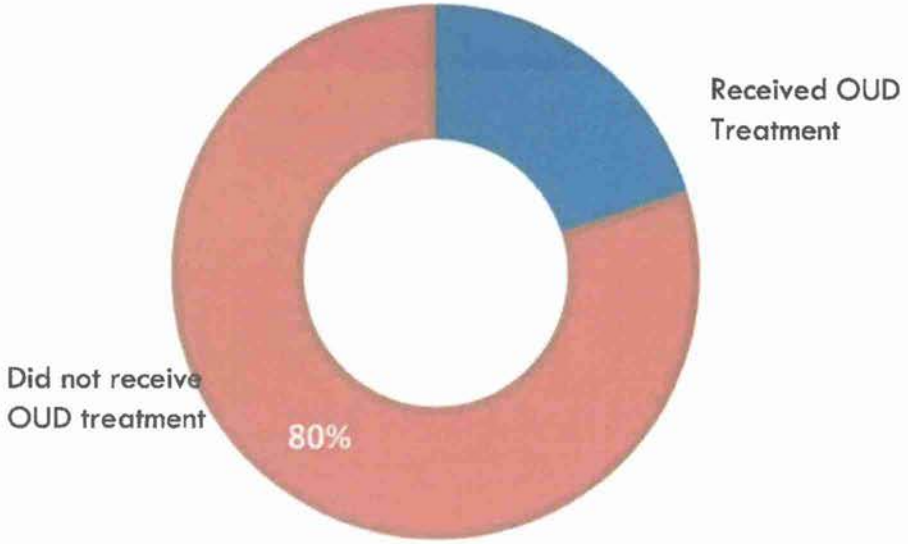
- Improved treatment retention
- Lower rates of other opioid use
- Improved social functioning
- Decreased injection drug use
- Reduced HIV and HCV transmission
- Better quality of life




Source: NASEM, 2019

# BUT ... Few with OUD receive treatment

**> 2 million Americans with Opioid Use Disorder**



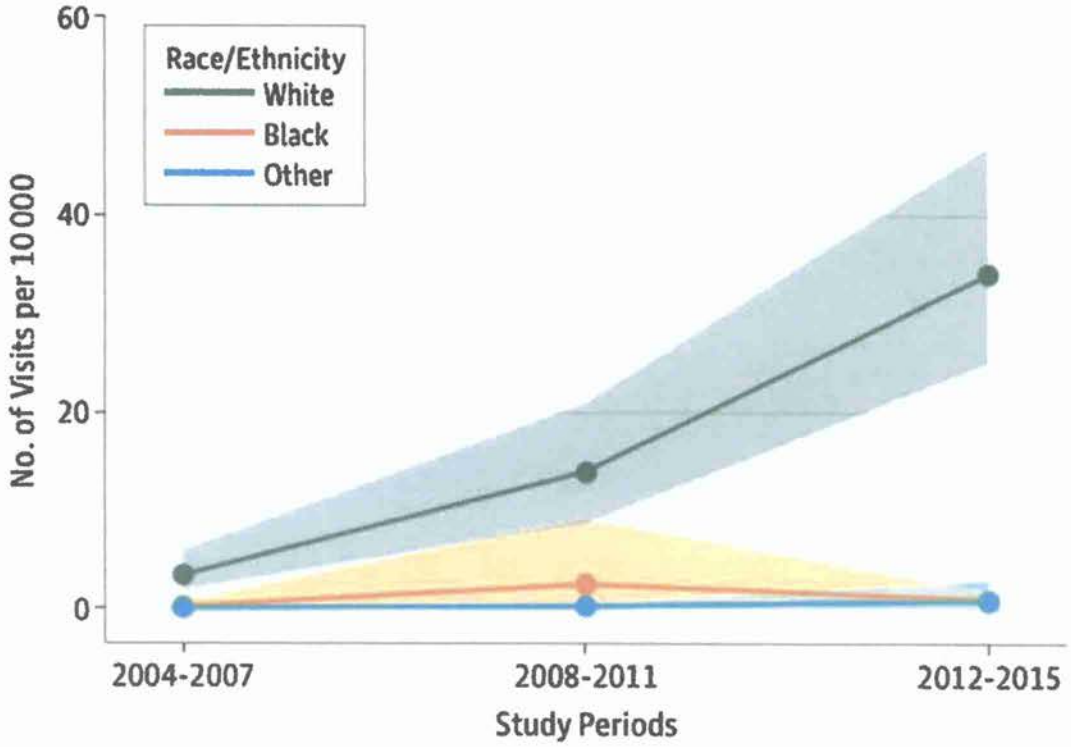

**What gets in the way?**

- Access challenges
- Programmatic rules and requirements
- Pharmacy barriers
- Stigma

NSDUH

# Disparities in Buprenorphine Care

Buprenorphine prescriptions higher among white, commercially insured patients




Hansen, 2013; Netherland 2018; Lagisetty, 2019

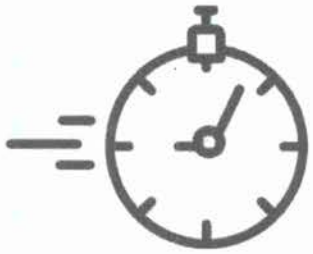
# What gets in the way?

| | |
|---|---|
| Didn't know where to go | 64% |
| Could not pay | 38% |
| No transportation | 30% |
| Treated poorly during OUD treatment | 13% |
| Didn't want to be seen at center | 13% |
| Did not trust physician | 5% |

Fox, 2015

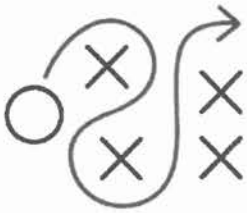
# What is Low-Barrier Treatment?

**"Medication First"** Approach



Rapid medication access

Harm reduction approach



Flexible treatment model

Non-traditional settings

Jakubowski and Fox, 2019

# Why Low-Barrier Care?

# Take Advantage of Reachable Moments

- Patients seeking addiction treatment are **more likely to be engaged** if they are **seen on the same day** compared to waiting 2+ days
- Starting buprenorphine in the ED in all-comers with OUD **more than doubles** retention in treatment at 30 days compared to referral alone

Roy, 2021; D'Onofrio, 2015

# Office-based buprenorphine without intensive counseling is effective

ORIGINAL ARTICLE

## Counseling plus Buprenorphine–Naloxone Maintenance Therapy for Opioid Dependence

David A. Fiellin, M.D., Michael V. Pantalon, Ph.D., Marek C. Chawarski, Ph.D., Brent A. Moore, Ph.D., Lynn E. Sullivan, M.D., Patrick G. O'Connor, M.D., M.P.H., and Richard S. Schottenfeld, M.D.

ABSTRACT

BACKGROUND

The optimal level of counseling and frequency of attendance for medication distribution has not been established for the primary care, office-based buprenorphine–naloxone treatment of opioid dependence.

METHODS

We conducted a 24-week randomized, controlled clinical trial with 166 patients assigned to one of three treatments: standard medical management and either once-weekly or thrice-weekly medication dispensing or enhanced medical management and thrice-weekly medication dispensing. Standard medical management was brief, manual-guided, medically focused counseling; enhanced management was similar, but each session was extended. The primary outcomes were the self-reported frequency of illicit opioid use, the percentage of opioid-negative urine specimens, and the maximum number of consecutive weeks of abstinence from illicit opioids.

Brief medically focused counseling vs

Intensive counseling interventions

**No difference**

Fiellin, 2006 NEJM; Carroll and Weiss, 2017

Penn
University of Pennsylvania

Center for Addiction Medicine and Policy

# Evidence from COVID

JAMA Network | Open.

Research Letter | Substance Use and Addiction

## Use of Telemedicine for Buprenorphine Inductions in Patients With Commercial Insurance or Medicare Advantage

Benjamin A. Barsky, ID MBE; Alisa B. Busch, MD MS; Sadiq Y. Patel, PhD MS; Ateev Mehrotra, MD; Haiden A. Huskamp, PhD

Original Investigation | Substance Use and Addiction

August 27, 2021

## Mobile Telemedicine for Buprenorphine Treatment in Rural Populations With Opioid Use Disorder

Eric Weintraub, MD[1]; Chamindi Seneviratne, MD[1]; Jessica Anane, MPH[1]; et al

## Telehealth for opioid use disorder treatn in low-barrier clinic settings: an explorat of clinician and staff perspectives

Shoshana V. Aronowitz[1*], Eden Engel-Rebitzer[2], Abby Dolan[3], Kehinde Oyekanmi[3], David Zachary Meisel[2], Eugenia South[2] and Margaret Lowenstein[2]

JAMA Psychiatry | Original Investigation

## Receipt of Telehealth Services, Receipt and Retention of Medications for Opioid Use Disorder, and Medically Treated Overdose Among Medicare Beneficiaries Before and During the COVID-19 Pandemic

Christopher M. Jones, PharmD, DrPH; Carla Shoff, PhD; Kevin Hodges, BS; Carlos Blanco, MD, PhD; Jan L. Losby, PhD, MSW; Shari M. Ling, MD; Wilson M. Compton, MD, MPE

## Utilizing telemedicine during COVID-19 pandemic for a low-threshold, street-base buprenorphine program

Robert Harris [a, b] ✉, Amanda Rosecrans [a, b], Meredith Zoltick [a, b], Catherine Willman [a, b], Ronald Saxton [a], Margaret Cotterell [a, b], Joy Bell [a, b], Ingrid Blackwell [a, b], Kathleen R. Page [a]

## Buprenorphine Telehealth Treatment Initiation and Follow-Up During COVID-19

Elizabeth A. Samuels MD, MPH, MHS ✉, Utsha G. Khatri MD, MSHP, Hannah Snyder MD, Rachel S. Wightman MD, Babak Tofighi MD, MSc & Noa Krawczyk PhD

Penn
University of Pennsylvania

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# Shift towards a "Medication First Approach"

Benefits of MOUDs are seen even with imperfect abstinence

Benefits of MOUDs are seen with or without intensive treatment with counseling, mutual aid, or other additional treatments

**Start medication whenever and wherever patients touch the health care system!**

# Low-Barrier Care in Policy

The NEW ENGLAND JOURNAL of MEDICINE

OCTOBER 13, 2022

**Transforming Management of Opioid Use Disorder with Universal Treatment**

Rahul Gupta, M.D., M.P.H., M.B.A., Rachel L. Levine, M.D., Javier A. Cepeda, Ph.D., M.P.H., and David R. Holtgrave, Ph.D.

**"A growing body of evidence supports 'low-threshold' buprenorphine treatment,** an approach that embraces the harm-reduction philosophy of meeting patients where they are … **Our agencies are working to expand funding for these services"**

Gupta, 2022

# Pilot Trial of Pharmacist-Led Treatment

NEJM

**Physician-Delegated Unobserved Induction with Buprenorphine in Pharmacies**

Patients in pharmacy-based program 5x more likely to to be retained at 1 month (89% vs 17%)

**Pharmacists can start patients on road to recovery from opioid use disorder, study shows**

A study in the New England Journal of Medicine showed that pharmacies can offer a safe and accessible treatment starting point for patients with opioid use disorder and keep them better engaged than usual care with a physician.

Center for Addiction Medicine and Policy

Department of Public Health

## W

to


Call to speak with a Substance Use Navigator who can help connect patients to care

**Objectives:**

- 100% Virtual
- Tele-Bupe
- Low Barrier
- Insurance not necessary

M- M

# Wrap-Up

- With the removal of the X-waiver, we have opportunities to expand buprenorphine access
- Growing evidence for low-barrier approaches
- How can we work with pharmacy partners to overcome barriers to treatment?

# Questions?

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DISEASES AND DISORDERS

# Current status of opioid addiction treatment and related preclinical research

M. J. Kreek*, B. Reed, E. R. Butelman

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**Opioid use disorders (OUDs) are diseases of the brain with behavioral, psychological, neurobiological, and medical manifestations. Vulnerability to OUDs can be affected by factors such as genetic background, environment, stress, and prolonged exposure to μ-opioid agonists for analgesia. Two standard-of-care maintenance medications, methadone and buprenorphine-naloxone, have a long-term positive influence on health of persons with opioid addiction. Buprenorphine and another medication, naltrexone, have also been approved for administration as monthly depot injections. However, neither medication is used as widely as needed, due largely to stigma, insufficient medical education or training, inadequate resources, and inadequate access to treatment. Ongoing directions in the field include (i) personalized approaches leveraging genetic factors for prediction of OUD vulnerability and prognosis, or for targeted pharmacotherapy, and (ii) development of novel analgesic medicines with new neurobiological targets with reduced abuse potential, reduced toxicity, and improved effectiveness, especially for chronic pain states other than cancer pain.**

## ADDICTION TO μ-OPIOID AGONISTS SUCH AS HEROIN, PRESCRIPTION OPIOIDS, AND FENTANYL ANALOGS

Opioid use disorders (OUDs), including their most severe form (opioid addiction), are a major public health challenge, in both industrialized and developing countries (*1*, *2*). Acute mortality from OUDs is related primarily to respiratory depression, modulated by μ-receptors in brainstem nuclei (*3*, *4*). Opioid-induced mortality is also often observed in persons who are exposed to multiple other substances, including alcohol, cocaine, and benzodiazepines (*5*). There are other major sources of morbidity and comorbidity in OUDs, and these include increased prevalence of infectious diseases (e.g., HIV/AIDS and hepatitis C) (*6*).

Smoking and ingestion of dried opium wax isolated from the poppy bulbs of *Papaver somniferum* have been occurring for millennia, for the purposes of medical pain relief and of achieving altered states of consciousness (*7*). Physical dependence following daily chronic use of opium, defined in the context of withdrawal symptoms upon abstinence, has been historically documented as early as the 16th century (*6*). Two discoveries in the 19th century were crucial for the improvement of analgesic therapeutics as well as leading to devastating consequences in terms of opioid addiction and potential for fatal overdose as a consequence of respiratory depression: the extraction of morphine (Fig. 1A) as the primary active ingredient of opium and the development of the hypodermic needle for intravenous administration (*7*). Heroin (Fig. 1B) was later developed as a semisynthetic derivative of morphine, involving diacetylation of the hydroxyl groups that leads to a 10-fold increase in potency in vivo, due to enhanced delivery to the brain (*8*). Heroin itself has limited affinity for μ-opioid receptors, but following distribution to the brain undergoes biotransformation, initially yielding primarily 6-acetyl morphine and then morphine as active metabolites (Fig. 2A).

Myriad derivatives of morphine have been synthesized in the quest for improved analgesics, beginning in the 19th century and continuing to this day. A prominent example of a drug developed as an improved analgesic is oxycodone (Fig. 1C). Oxycodone is synthesized from opium extracts of thebaine as a starting point (*9*). As can be seen from Fig. 1, oxycodone is structurally similar to morphine, sharing a common backbone structure, referred to as a morphinan. Although oxycodone has been in clinical use since shortly following its initial synthesis and characterization in the 1910s, its use increased vastly with the development of a patented 12-hour extended-release formulation, introduced in 1996, and enhanced marketing and prescriptions for pain therapy (*10*). Other common morphinans that are medically approved analgesics but are commonly misused include morphine (Fig. 1A), hydrocodone, and oxymorphone (*11*).

Synthetic compounds with considerable structural deviation from the classical morphinans also have μ-opioid agonist effects. Fentanyl (Fig. 1D), for instance, is a selective μ-opioid receptor agonist with high in vivo potency. Fentanyl was approved by the Food and Drug Administration (FDA) in 1968 and is available for perioperative intravenous or epidural/intrathecal administration, as well as in various other formulations for take-home use, including transdermal patches, buccal film, buccal spray, buccal tablet, nasal spray, and lozenges.

Various fentanyl analogs have also been approved for use in specific situations. Remifentanil was approved by the FDA in 1996 and is used in intravenous formulation during anesthesia. Sufentanil, approved initially in 1984, is similarly used perioperatively in conjunction with anesthesia and is also used epidurally for pain relief during labor and delivery. Very recently, a new sublingual tablet formulation of sufentanil was approved by the FDA for the treatment of acute pain, in medically supervised health care settings. Alfentanil was also approved for use in 1986 for perioperative intravenous administration in conjunction with anesthetics. Another analog, carfentanil, is used in veterinary medicine for large mammals and also as a positron emission tomography (PET) radiotracer (*12*). The potency of carfentanil makes it particularly dangerous, with a high potential for overdose, when abused by humans.

In recent years, there has been an increasing problem with production of fentanyl and its analogs in different countries including Mexico and China (*13*) and with these products entering the United States across borders and by mail (*14*–*17*). Fentanyl and its analogs

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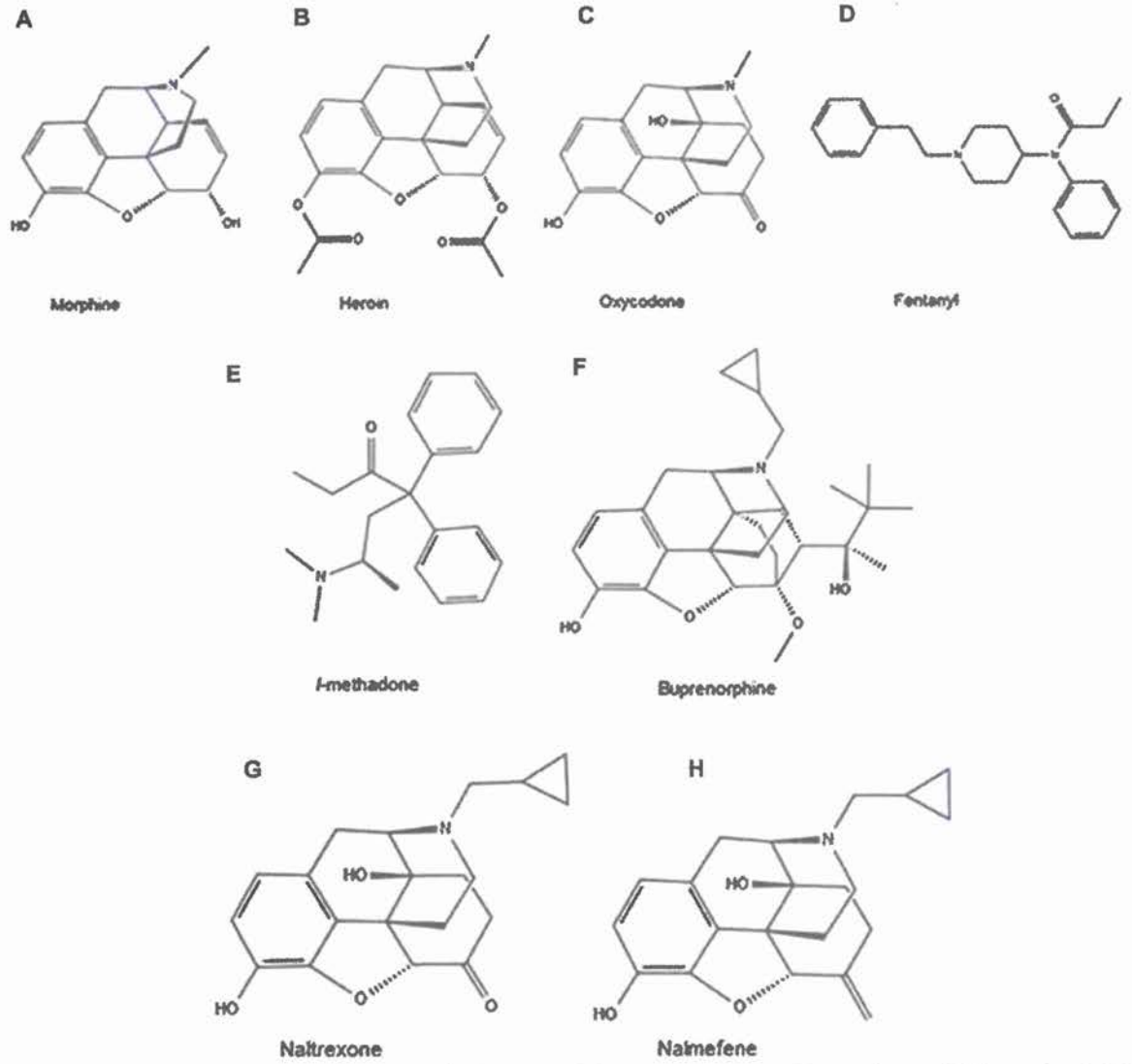


**Fig. 1. Chemical structures of the most commonly abused opioids.** Structures of (**A**) morphine, (**B**) heroin, (**C**) oxycodone, and (**D**) fentanyl and of the opioidergic therapeutics methadone (**E**) and buprenorphine (**F**). In addition, shown are antagonists naltrexone (**G**) and nalmefene (**H**). The structurally similar morphinan derivatives (A, B, C, F, G, and H) derived from opium, or synthesized from thebaine obtained from opium, contrast sharply with the structures of the synthetic opioids methadone and fentanyl (E and D, respectively).

have thus become "street" drugs, occasionally sold illicitly alone, and, more commonly, as additives to heroin (*16*) to increase the perceived potency of the latter. These synthetic compounds have been a major cause of recent increases in overdose deaths (see Fig. 3) (*18*).

### The impact of excessive availability of prescription opioids

Medical and nonmedical use of prescription opioids, such as oxycodone, have been increasing markedly, especially in the United States (*19*), either in the patient to whom the medication was originally prescribed or frequently by someone else taking the unused medicine. This increase has occurred in part as a result of the World Health Organization's reduced oversight of international sales and movement of opiates, beginning in the late 1980s. Further exacerbating this problem, recent changes in U.S. medical practice have encouraged physicians to prescribe "as much medication as any patient needs for relief of their pain" (a concept foreign to U.S. medical education until the mid-1990s), accompanied by extensive promotion and marketing of some opioid formulations during the same period. These factors have led to a marked change in physician prescription habits, from earlier prescriptions of 3 to 7 days of opioids for acute pain (such as surgical procedures and fractures) to current averages of pain medications up to 3 weeks or even longer (*20*). This increase has created a large excess of prescription opioids available for misuse, which can then progress to OUDs and use of illicit drugs such as heroin (*21*, *22*).

## EPIDEMIOLOGY

The most recent data from the federal government, primarily from the Substance Abuse and Mental Health Services Administration, the National Institute on Drug Abuse (NIDA), and the National Household Survey on Drug Abuse and Health, as well as Monitoring the Future,

A

| | Systemic bioavailability after oral administration | Apparent plasma terminal half-life ($t_{1/2}$ beta) | Major route of biotrans-formation |
|---|---|---|---|
| Heroin | Limited (<30%) | 3 min (30 min for active 6-acetyl-morphine metabolite; 4–6 hours for morphine and active morphine-6-glucuronide metabolite) | Successive deacetylation and morphine glucuronidation |
| Methadone | Essentially complete (>70%) | 24 hours (48 hours for active [R](i)-enantiomer) | *N*-demethylation |

B

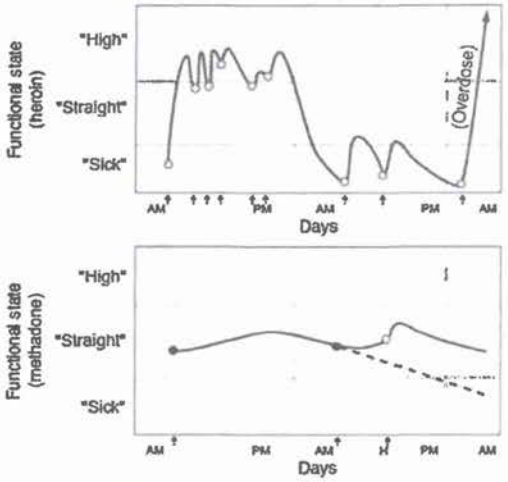


**Fig. 2. Heroin addiction contrasted with methadone maintenance.** (**A**) Difference in plasma protein binding and metabolism results in substantially different pharmacokinetic profiles and bioavailability for heroin versus methadone (*55*). (**B**) Prototypic administration pattern and subjective state for heroin versus methadone. Multiple doses of heroin are self-administered daily to achieve a state of "high" (euphoria) or, in cases with a depleted supply, to avoid a feeling of "sick" (withdrawal). Methadone, at steady state with single daily administration, leads neither to subjective states of high nor sick (*43*).

show that over 16 million people in the United States suffer from some addictive disease (see Table 1). The most common addiction is alcoholism, followed by addiction to cannabis, opioids, and cocaine.

At least 1 million to 2 million persons in the United States suffer from addiction to heroin and other short-acting opioids (Table 1). It is estimated that over 37 million persons have misused short-acting opioids such as oxycodone and hydrocodone. The number of persons who have become addicted to these compounds has only been roughly calculated. Some epidemiological data show that approximately 20% of persons who self-administer a prescription opioid for nonmedical use will develop an OUD (*23*). In the past two decades, increasing numbers of people who started with misuse of prescription opioids (e.g., oxycodone) then commence the use of heroin because it is cheaper than illicit sales of these prescription opioids (*24*). In the past 5 years, the number of overdose deaths in the United States has risen to approximately 50,000/year. For example, in New York City alone, it has recently been estimated that there are

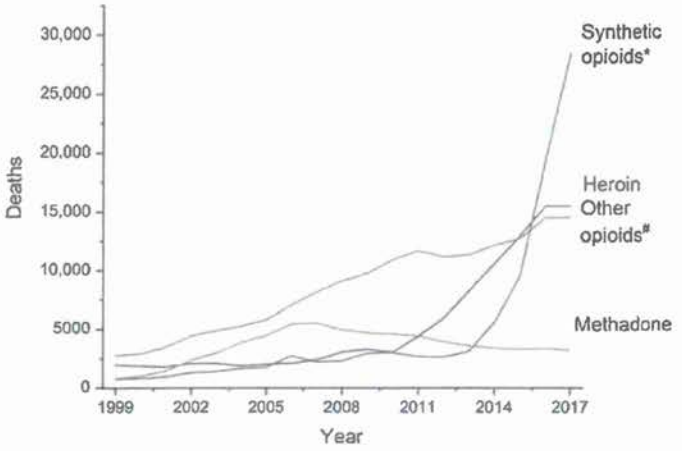


**Fig. 3. Opioid overdose deaths in the United States, 1999–2017.** Data from Centers for Disease Control and Prevention, 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes. Asterisk indicates synthetic opioids other than methadone, e.g., prescribed or illicit fentanyl, fentanyl analogs, and tramadol. Number sign indicates natural or semisynthetic opioids other than heroin, e.g., morphine, oxycodone, and hydrocodone.

approximately four overdose deaths each day (*25*). There have been substantial increases in opioid-induced overdose deaths in recent years, especially those involving heroin and fentanyl (*18*, *26*). This statistic includes a widening "gender gap," in which overdose vulnerability in males is increasing more than in females (*18*).

## PUBLIC HEALTH NEED FOR INCREASE IN AVAILABILITY OF MEDICATION-BASED TREATMENT OF OPIOID ADDICTION

Because of the major stigma of drug abuse, there has been an almost complete absence in most medical schools of education about opioid addiction, its diagnosis, treatment of overdose, and chronic pharmacotherapy (*27*, *28*). More broadly, most medical schools have only limited education about any other addictive disease as well.

The number of persons in methadone maintenance treatment programs (MMTPs) in the United States is approximately 382,000, while the number of persons in buprenorphine-naloxone treatment is approximately 112,000 (see Table 2). In the entire world, the number of people in MMTP is currently roughly 1.4 million (see table S1). For the less effective treatment with naltrexone (either as a daily oral medication or in depot injection formulation) (*29*), 23,000 persons are currently in treatment in the United States. Many of these persons entered naltrexone treatment due to the criminal justice system or due to regulations on physicians that exist in some (but not all) states.

Studies have shown that fewer than 10% of persons with opioid addiction are able to achieve long-term abstinence without medication-assisted treatment with methadone or buprenorphine maintenance (*30*). No behavioral or cognitive treatments alone have been shown to be effective for patients with opioid addiction (or severe OUD).

It is disturbing that the number of persons in medication treatment overall remains very low, given the numbers afflicted with opioid addiction. However, in 2017, there appears to have been a modest increase in numbers of persons in both MMTP and buprenorphine-naloxone treatment, following a decrease in 2016 (see Table 2).

**Table 1. Epidemiology of drug use.** Prevalence of specific drug abuse and vulnerability to develop addictions. SAMHSA National Survey on Drug Use and Health, 2017; others 2007–2018.

| National household survey and related surveys (2007–2016) | |
|---|---|
| Heroin use—ever | ~5.2 million |
| Heroin addiction | ~652,000 |
| Illicit use of opiate medication—ever | ~37.1 million (i.e., 14.2% of the population 12 and over) |
| Dependence on such medication use | ~2.1 million |
| Opiate (heroin, fentanyl, and other) overdose deaths | ~72,3000 (in 2017)* |
| Cocaine use—ever | ~40.5 million |
| Cocaine addiction | ~966,000 |
| Alcohol use—ever | ~216 million |
| Alcoholism | ~14.5 million |
| Marijuana use—ever | ~123 million |
| Marijuana daily use | ~4 million |
| **Development of addiction after self-exposure** | |
| Opiate addiction | ~1 in 5 to 1 in 15 (20 to 6.5%) |
| Alcoholism, marijuana, and cocaine dependency | ~1 in 8 to 1 in 15 (12.5 to 6.5%) |

*National Center for Health Statistics (U.S. Centers for Disease Control and Prevention), 2019.

**Table 2. Status of methadone, buprenorphine, and extended-release naltrexone treatments for opioid addiction in the United States: Decrease and then increase in numbers in treatment 2015–2017 (SAMHSA, 2018).**

| Treatment | U.S. patients in treatment | | |
|---|---|---|---|
| | 2015 | 2016 | 2017 |
| Methadone maintenance | 356,843 | 345,443 (–11,400; –3.2%) | 382,867 (+37,424; +10.8%) |
| Buprenorphine maintenance | 75,723 | 61,486 (–14,237; –18.8%) | 112,223 (+50,737; +82.5%) |
| Extended-release naltrexone | 7035 | 10,128 (+3093; +44.0%) | 23,065 (+12,937; +128.7%) |

The major known factor contributing to the effectiveness of medication-assisted treatment is compliance in taking the medication daily. Compliance is not an issue with methadone maintenance treatment because federal regulations mandate that patients in treatment visit the clinic initially daily to receive their methadone dose, which can be reduced to weekly or monthly visits when a patient has been in successful long-term treatment (medical maintenance). That said, the strict federal regulations surrounding methadone maintenance have had the consequence of limiting the number of clinics and therefore reduce the availability of effective treatment to those in need. Buprenorphine must also be used daily but, under federal law, can be prescribed for up to 30 daily doses at a time, with the patients responsible for self-administering their daily dose.

Research over the past 50 years shows that the most critical need in the treatment of opioid addiction is the continued and expanded availability of treatment with a long-acting steady-state medication (μ-opioid receptor agonist or partial agonist). Research has documented that a relative "endorphin deficiency" develops in persons with long-term opioid addiction (*31*). Therefore, treatment with methadone or buprenorphine maintenance can be considered a long-term "replacement" therapy similar to thyroxin treatment for thyroid deficiency or insulin use for diabetes.

## Criteria for OUD diagnosis

OUD is currently defined by the DSM-5 (fifth edition of the Diagnostic and Statistical Manual; www.DSM5.org), based on the number of clinical criteria that are met (*32*). Increasing numbers of criteria met can be used to qualify the diagnosis as mild, moderate, or severe. These criteria focus primarily on escalating self-exposure, tolerance, physical dependence, withdrawal, loss of control over intake, and proneness to relapse unless managed with chronic medication and related treatment. Several μ-receptor populations in brain, alone or in combination with other receptor systems, may mediate these different effects clinically and in translationally relevant models. Overall, the etiology of OUDs is multifactorial, and different types of mechanisms can contribute to vulnerability (see Fig. 4 and fig. S1).

## Development of physical dependence and withdrawal

After repeated exposure to μ-agonists, either in the context of medical prescription for analgesia or self-administration for nonmedical uses, a state of dependence develops. Withdrawal signs observed upon drug discontinuation include autonomic signs (e.g., piloerection, diarrhea, and changes in thermoregulation); sensory changes, including hyperalgesia; subjective anxiety-like effects; and neuroendocrine effects [e.g., increases in circulating levels of stress/hypothalamic-pituitary-adrenal axis hormones, adrenocorticotropic hormone (ACTH), and cortisol] (*33*). These diverse signs of withdrawal can be mediated by different neurobiological systems. Studies show that withdrawal can contribute to increased self-administration of μ-agonists (*34*), after the initial chronic exposure period.

The molecular and physiological underpinnings of μ-agonist dependence and withdrawal have been examined for decades. While several medications can be used to medically manage the severity of withdrawal (including the $\alpha_2$-adrenergic agonists clonidine or lofexidine) (*35*), the impact of the cycles of self-administration and withdrawal in OUDs remains a challenge and contributes to the continuation of the disease process. Some findings suggest that changes in μ-receptor signal transduction, as well as receptor cycling and internalization, occur after repeated exposure to μ-agonists (*36*). However, it is also clear that some withdrawal mechanisms develop on the basis of changes to neurobiological networks, which are downstream from μ-receptors (*37*, *38*). Withdrawal signs (and other interoceptive signs) can function as triggers to drug-taking and changes in reward function (*34*, *39*). The process of escalation of μ-agonist self-administration has also been examined in preclinical models (*40*).

## Basic function of μ-opioid receptors

μ-opioid receptors are $G_i/G_o$-coupled receptors [G protein (heterotrimeric GTP-binding protein)–coupled receptor], encoded by the gene *OPRM1* (*41*), and their main endogenous ligands are β-endorphin and enkephalin-derived neuropeptides (encoded by

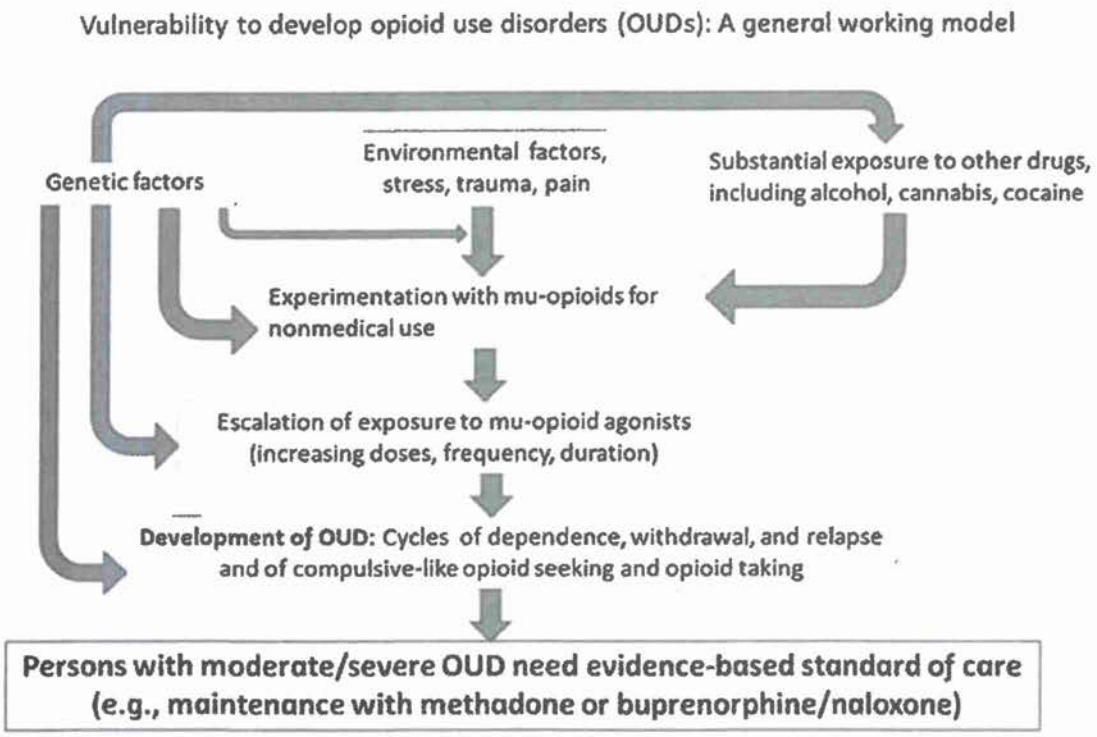


**Fig. 4. Model of the progression from misuse of opioids toward moderate or severe OUD (i.e., opioid addiction).**

*POMC* and *PENK*, respectively) (*42*, *43*). μ-receptors are located in several areas of the central nervous system (CNS) and also the gastrointestinal tract, where they can modulate diverse biobehavioral functions including reward, mood, anxiety, neuroendocrine function, and also gastrointestinal motility (*44*). μ-receptor systems also interact with other major neurobiological systems, such as dopaminergic, glutamatergic, and neuropeptide systems, including the κ-opioid receptor/dynorphin system (encoded by *OPRK1* and *PDYN*, respectively).

### Molecular changes in brain after repeated exposure to short-acting μ-opioid agonists

Several studies have shown that repeated exposure to μ-agonists such as morphine, heroin, or oxycodone can cause changes to mRNA expression of numerous targets, including prodynorphin and κ-receptor genes (*Pdyn* and *Oprk1*, respectively) (*45*, *46*). Using an mRNA array, it was found that several genes encoding neurotransmitter receptors (especially the γ-aminobutyric acid type A receptor β2 subunit; *Gabrb2*) were altered in the striatum after chronic oxycodone self-administration in adult mice (*47*). Other studies also show that molecular adaptations in the striatum and hippocampus differ between adult and adolescent mice, after chronic oxycodone self-administration (*48*, *49*). For example, expression of some genes, such as monoamine oxidase a (*Maoa*), was up-regulated in the dorsal striatum of both adult and adolescent mice, after chronic oxycodone self-administration. However, other striatal genes, especially gastrin-releasing peptide receptor (*Grpr*), were differentially regulated after chronic oxycodone self-administration in adults and adolescents (*48*, *49*).

Our laboratory has also recently reported RNA sequencing (RNA-seq) studies in the dorsal and ventral striatum (i.e., caudate-putamen and nucleus accumbens, respectively), which allowed an unbiased analysis of all targets affected after 14-day chronic oxycodone self-administration in adult mice (*50*–*52*). Focusing on neurotransmitter and neuropeptide systems, RNA-seq studies demonstrate that chronic oxycodone self-administration caused a change in pro-opiomelanocortin (*Pomc*), 5HT2a and 5HT7 receptors, galanin receptor, and glycine receptor. RNA-seq also shows that chronic oxycodone self-administration causes up-regulation of 54 and 126 genes involved in neuroinflammation/immunomodulation in the dorsal and ventral striatum, respectively (*50*). In addition, genes involved in axon guidance, in the integrin, semaphorin, and ephrin systems, were differentially altered in both the dorsal and ventral striatum, after chronic oxycodone self-administration (*51*). These RNA-seq data describe the complex gene regulation that occurs in the brain of subjects, which self-administered oxycodone over a relatively prolonged period, and indicates some of the brain processes that could be affected in persons with severe OUD.

Furthermore, some of the aforementioned molecular changes can persist or even emerge well after exposure to the μ-agonist is discontinued (*46*). The aforementioned studies show that repeated μ-agonist exposure results in complex and potentially long-lasting neuroadaptations that could underlie different aspects of opioid addiction and its relapsing features. Interventions on some of these molecular targets may be fruitful avenues for the development of mechanism-based prevention of opioid addiction or to minimize neural remodeling that may occur after iatrogenic exposure to μ-agonists.

## CURRENT TREATMENT FOR OPIOID ADDICTION

### μ-opioid agonist and partial agonist medications

#### *Methadone*

Research on developing a treatment for opiate addiction came to fruition at the Hospital of the Rockefeller Institute for Medical

Research in 1964 by Dole *et al.* (*53*). The treatment developed was methadone maintenance treatment, approved by the FDA in 1972, which remains the most widely used effective therapeutic approach for opioid addiction (Table 3) (*54*–*56*).

In good-quality MMTPs, which provide adequate counseling, medical, and psychiatric care (which pertains in most local and national legislations and rules), 60 to 80% of persons can respond well, stay voluntarily in treatment for more than 1 year, and progressively decrease the use of illicit opioids over the first 3 to 6 months (*57*). However, approximately 20 to 40% of persons may drop out of treatment. In individuals receiving chronic oral methadone, intravenous or parenteral methadone does not cause euphoria (or high) because it rapidly binds to plasma proteins (*53*).

Methadone maintenance has greater retention than buprenorphine maintenance (see below), probably because the former is a full agonist at the μ-opioid receptor and also has modest *N*-methyl-D-aspartate receptor antagonist activity, which may further retard the development of tolerance (*58*, *59*). Methadone needs to be used in moderate to high doses, usually 80 to 150 mg/day, to create sufficient cross-tolerance to "blockade" the euphoric effects by superimposed short-acting μ-agonists.

**Table 3. FDA-approved medications for OUD, with typical dosing paradigms for each of the approved formulations.** PO, per os (oral); SL, subligual; BUC, buccal; SQ, subcutaneous; IM, intramuscular.

| Treatment | Dose range | Considerations |
|---|---|---|
| Methadone (PO) | 80–150 mg/day (typical range) | Maintenance dosing is determined during the early weeks of treatment following upward titration. Individual genetic and drug history differences may lead to requirement of higher doses than the typical range. FDA approved in 1972. |
| Buprenorphine-naloxone (SL or BUC) | 8–24 mg/day buprenorphine (1–6 mg/day naltrexone) (typical range) | 4:1 ratio (w/w) of buprenorphine-naloxone. Because of partial agonist nature of buprenorphine, no further treatment effect to be gained by doses greater than 24 mg/day. FDA approved in 2002. |
| Buprenorphine extended-release formulation (SQ) | 80–300 mg/monthly injection | Two formulations available. FDA approved in 2016 and 2017. |
| Naltrexone tablets (PO)/extended-release formulation (IM) | 50 or 100 mg/day orally; 380 mg/monthly IM injection | Requires a patient to be opioid free for 7–10 days before administration. FDA approved in 1984 (tablets, no longer marketed); 2010 (extended release). |

Methadone, when administered orally, has a slow onset and offset of action. When used to treat opioid addiction, moderate doses of methadone should be used initially (30 to 40 mg/day) and slowly increased, usually at the rate of 10 to 20 mg/week up to a daily dose that provides cross-tolerance to the effects of any superimposed short-acting μ-agonist, i.e., "narcotic blockade," while preventing opioid withdrawal signs without causing euphoria (Fig. 2B) (*53*). With the increasing purity of heroin over the past two to three decades, the optimal treatment dose in most patients with opiate addiction is 80 to 150 mg/day, with higher doses needed in a small percentage of patients. These doses of methadone are markedly higher than those used to treat chronic pain, which usually range from 10 to 45 total mg/day, delivered in divided doses. Because of extensive binding to plasma protein, as well as to tissues, methadone enters the brain slowly and exits the brain slowly, allowing a steady state to develop (*60*). The half-life of racemic methadone (the usual form) in humans is approximately 24 hours (±4 hours). The half-life of the active enantiomer (*l* or R, Fig. 1E) is around 48 hours, and the half-life of the inactive enantiomer (*d* or S) is around 16 hours (*61*–*63*). Methadone is biotransformed to pyrolline and pyrrolidine metabolites, both inactive and excreted primarily not only in urine but also in feces. Methadone does not cause enhanced or inhibited microsomal activity. Therefore, doses of methadone can be kept constant for at least 10 years with little need for change. With a half-life for the racemic formulation of 24 hours, steady-state methadone can be achieved with once daily dosing of a specific dose within 1 week. PET investigations of formerly heroin-addicted individuals, maintained on steady-state methadone at an effective treatment dose, indicate that the occupancy of the μ-opioid receptor is not close to 100% but rather 30 to 40% (*64*).

### *Buprenorphine*

Buprenorphine was originally developed in the 1970s as an analgesic (Fig. 1F) in the laboratory of J. Lewis, at Reckitt-Colman in the United Kingdom. When used as a maintenance medication for OUD, buprenorphine must be used by the sublingual, but not oral route, due to rapid liver biotransformation. Unfortunately, when used parenterally or injected intravenously, buprenorphine can have euphoric effects. However, it has also been shown that the addition of naloxone in the sublingual formulation of buprenorphine, if self-administered parenterally, prevents this euphoria for at least 30 min (i.e., the half-life of naloxone) (*65*). Very recently, sustained release implants of buprenorphine have been developed that last up to 30 days (Table 3) (*66*).

Buprenorphine and buprenorphine-naloxone are also effective for at least 6 months in at least 40 to 50% of unselected patients (*67*). The sublingual formulation with the largest buprenorphine dose (12 mg) is combined with 3 mg of naloxone. The FDA-approved package insert states that sublingual doses of buprenorphine larger than 24 mg have not been shown to have a further clinical advantage. As above for methadone, it is critical that buprenorphine maintenance doses should be sufficient to achieve blockade of short-acting μ-opioid agonists (*68*).

Buprenorphine administered by the sublingual route has an extended half-life compared to the half-life of intravenous buprenorphine, which is similar to short-acting opiates, and has also been shown to bind to the μ-opioid receptor with slow dissociation kinetics (*69*). Therefore, in treatment of addiction, buprenorphine has a sustained

effect, as does methadone, but for different reasons. Rapid "on-off" effects of a μ-agonist affect signal transduction and result in adaptations including desensitization and tolerance (*70*). Maintenance with methadone orally or buprenorphine sublingually provides steady-state occupancy at μ-opioid receptors (*12*, *64*), with limited tolerance, as shown by stable doses in the clinic, over prolonged periods. Since buprenorphine is a μ-receptor partial agonist with dissociation kinetics, it can block binding of other self-administered μ-opioid agonists. PET studies reveal that buprenorphine maintenance results in submaximal occupancy of brain μ-receptors (40 to 60%) (*12*). This maintenance treatment is able to block the effects of challenge with short-acting μ-agonists (*68*).

### Opioid antagonist medications

As mentioned previously, naltrexone (Fig. 1G) has been approved as a treatment for opioid addiction, both with oral tablet administration and more recently intramuscular depot injections with sustained release for approximately 1 month (Table 3) (*71*). Naltrexone is primarily a μ-antagonist and is also a κ-opioid receptor partial agonist (*72*). Acute administration of naltrexone to a person who is actively dependent on μ-agonists results in precipitated withdrawal symptoms, which are aversive. Thus, prior to naltrexone induction, patients must be withdrawn from μ-agonists first, with several days of abstinence, initiated with or without tapering.

Daily oral naltrexone has been of only limited utility in the treatment of OUD-related morbidity (*29*). So far, only a few studies of limited duration have been performed on intramuscular depot naltrexone, designed to provide stable levels of naltrexone for approximately 1 month [for example, (*73*–*75*)]. The long-term clinical impact is still unclear (*29*). Depot naltrexone can block the effects of short-acting μ-agonists (*76*). However, to our knowledge, depot naltrexone has not been shown to normalize the persistent neurobiological changes that result from long-term exposure to illicit opioids.

Depot naltrexone could be potentially useful as a therapeutic modality before onset of multiple daily opioid use (a characteristic of dependence and addiction) before the development of persistent neurobiological disruptions. There is some concern that hepatotoxicity may result from chronic long-term naltrexone use, at least in a subset of patients. As an alternative, a similar compound, nalmefene (Fig. 1H), may also be useful in a depot formulation in the future. At this time, nalmefene is administered in oral formulation, as an "as-needed" medication for the treatment of alcohol use disorder, and approved for use in Europe and Japan. Nalmefene, similar to naltrexone, is a μ-opioid receptor antagonist and also has κ-partial agonist effects, primarily through G protein signaling (*77*, *78*).

The most commonly used opioid antagonist against overdose is currently naloxone, which is of lower potency and shorter duration of action, compared to its congeners, naltrexone, and nalmefene. Naloxone has been of major importance for saving thousands of lives in overdose situations. With the recent availability of illicit fentanyl and its analogs, due to their enhanced potency and longer duration of action, single doses of naloxone are not always effective in rescuing opioid-induced respiratory depression (*79*). Multiple sequential injections of naloxone are sometimes necessary, particularly with fentanyl analogs. Naltrexone and nalmefene, which have longer durations of action, are therefore receiving current attention as anti-overdose medications against potent fentanyl analogs (*80*).

Long-acting medications such as methadone and buprenorphine-naloxone can be used on a long-term basis with little dose change. Long-acting medications allow normalization of functions in humans that are disrupted by short-acting μ-agonists, including stress responsivity and hormone-regulated reproductive function (specifically normalization of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes) (*81*, *82*).

### Human molecular genetics related to opioid use disorders

#### *Variants of the μ-receptor gene, Oprm1*

In 1998, we reported on an important and fairly common single-nucleotide polymorphism (SNP) of the μ-opioid receptor, the A118G variant, which changes an amino acid in the N terminus (*83*). In collaboration with Yu and colleagues (*83*), we showed that the A118G variant results in increased binding affinity of the endogenous neuropeptide, β-endorphin. We and others also showed that with this variant, there is greater signal transduction to the G protein–coupled inwardly rectifying potassium channel system.

In the initial clinical studies, we and others learned (*83*) that this A118G variant occurs in around 8 to 30% of European Caucasian populations and occurs in 40 to 60% of Asian populations. However, it is not present in African populations, unless admixture has occurred. Further work from our laboratory, carried out in collaboration with the Karolinska Institute (Stockholm, Sweden), showed that A118G is strongly associated with opioid addiction (*84*) and with alcoholism (*85*). Each of these findings was made in a European Caucasian population. Several other groups have also studied this variant in healthy humans and have found that one or two copies of the G nucleotide result in altered stress responsivity, including altered responsivity to a challenge with a μ-receptor antagonist, which normally activates this system (*86*, *87*). Further, it has been shown that one or two copies of this variant markedly alter the response in normal volunteers to metyrapone, a neuroendocrine test compound that cuts off the production of cortisol by the adrenal cortex for about 8 hours, resulting usually in a surge of β-endorphin and ACTH (*88*). This effect arises because the normal negative feedback system by cortisol or other glucocorticoids is temporarily blocked. Thus, in persons with one or two copies of the A118G variant, a subnormal response to metyrapone testing was observed. This response is likely due to changes in β-endorphin binding to the μ-receptor in carriers of this variant, as this neuropeptide is part of the modulation of stress responsivity. Thus, with higher affinity binding of β-endorphin to the G variant–carrying μ-opioid receptor, one sees less activation of the stress axis, resulting in lower ACTH (and likely β-endorphin) levels after metyrapone challenge.

In addition, transgenic mice homozygous for the G variant self-administer over twice as much heroin (than the wild-type) (*89*). These findings show that even a single amino acid change in the coding region of the μ-opioid receptor can significantly increase the amount of self-administered short-acting μ-agonist.

Methadone and buprenorphine-naloxone maintenance treatment has been found to be effective in individuals with the *Oprm1* A118G polymorphism and with several other polymorphisms in genes expressed in brain (*90*). The effectiveness of this treatment is probably due to the relatively high dose of both medications that are used in the treatment of opioid addiction. However, polymorphisms of genes involved in methadone pharmacokinetics are associated with differences in the dose required for effective maintenance (*91*, *92*). Some studies have suggested that patients with one or two copies of the A118G variant may respond differently from those with the prototype both to pain and to analgesic treatment

with a μ-opioid receptor agonist (*93*). Both methadone and buprenorphine can be effectively used in the treatment of pain at relatively low doses, compared to maintenance doses used in OUDs. To our knowledge, no study has shown a difference in analgesic effects of these two compounds in persons with one or two copies of the A118G variant.

***Variants of the κ-opioid receptor (Oprk1) and prodynorphin (Pdyn) genes***

A second group of gene variants that have been shown to be associated with different addictive diseases is the functional 68–base pair (bp) repeat present in one to four copies in the promoter of the prodynorphin (*PDYN*) gene, which encodes for the endogenous neuropeptide at κ-opioid receptors (*94*). Some studies have found an association of this polymorphism with aspects of opioid addiction (*95*, *96*) in Caucasian populations, and similar findings of association of the number of 68-bp repeats have been reported in studies of the genetic determinants of cocaine addiction (*97*).

***Variants of cannabinoid system genes***

One laboratory has reported an association of fatty acid amide hydrolase gene variant 385C > A with opioid addiction (*98*). However, our laboratory was unable to confirm this finding in a larger sample of normal volunteer Caucasians, compared with those with opioid addiction, although we found several intriguing associations of polymorphisms of the cannabinoid receptor type 1 and opioid addiction (*99*). Across three different ethnicities studied (Caucasian Europeans, African-Americans, and Hispanics), a highly significant association was found of long repeats with heroin addiction ($P = 0.009$). Further, pointwise significant association of the allele 1359A ($P = 0.006$) and genotype 1359AA ($P = 0.034$) was associated with protection from heroin addiction in Caucasians.

***Variants of nociceptin/orphanin FQ receptor genes***

Our laboratory investigated the nociceptin/orphanin FQ receptor gene (OPRL1) with respect to genetic variants that might be associated with opioid addiction (*100*). In Caucasians, but not in African-Americans, we found that rs6090041 and rs6090043 variants of the *OPRL1* gene were significantly associated pointwise with opioid addiction. Of the haplotypes formed by these two variants, one was associated with vulnerability to develop opioid addiction in Caucasians (pointwise $P = 0.020$), and another haplotype of these variants was associated with protection from developing opioid addiction in African-Americans (pointwise $P = 0.04$).

***Recent human genetics of opioid addiction***

Our laboratory conducted a very early (2010) genome-wide association study to identify gene variants that might contribute to the risk for developing heroin addiction (*101*). SNPs in several genes encoding for components of the endogenous opioid system, neurotransmitter systems, and the stress hormone system were associated with heroin addiction in multiple ethnicities (see table S2) (*101*, *102*).

## Current research areas that have clear translational potential for the development of new treatments or interventions

In addition to the aforementioned approved medications, some current research areas may have translational potential. Promising research areas include the development of novel analgesic moieties with decreased abuse potential or with reduced risk of toxicity or overdose. These developments are the product of decade-long research efforts in public and privately funded research in medicinal chemistry and pharmacology (both in vitro and in vivo, in rodents and nonhuman primates).

Current areas of development include the examination of "biased" μ-agonists, which may potentially have an improved profile (e.g., a relatively lower propensity to cause constipation, respiratory depression, or abuse potential) compared to classic μ-agonists such as fentanyl (*103*, *104*). At this time, the superior characteristics of these agonists have not been demonstrated unequivocally (*105*). A second approach examined recently in preclinical models involves novel μ-agonists that would be active preferentially at the local site of injury or inflammation (e.g., at μ-receptors in the periphery) (*106*), thus diminishing risk of overdose and abuse potential, as the latter effects are mediated by receptors in the CNS.

A third approach has examined dual targeting of μ-opioid receptors and other receptors. One recent notable example, studied preclinically, is a dual μ-agonist/orphanin-agonist compound, which shows enhanced analgesia with a reduced burden of both respiratory depression and abuse potential (*107*).

More broadly, it has been shown that classic μ-agonists are not optimal for the chronic treatment of pain that is mediated by neuropathic or inflammatory mechanisms (*108*). Therefore, there has been a continued focus on novel pharmacological targets (i.e., not directed to the μ-receptors) for the chronic treatment of these kinds of pain.

## Gaps in scientific knowledge and research directions that are likely critical for advancing the effectiveness in treatment and recovery

The goals and rationale for pharmacotherapy for opioid addiction (*53*) are for a pharmacotherapeutic agent (preferably used orally or sublingually) to prevent withdrawal symptoms, to reverse drug craving, and to normalize any functions that have been disrupted by chronic drug use, especially brain function (*54*). Further, the medication should be targeted to a specific site of action, a specific physiological system affected or deranged directly by the drug of abuse, and not simply symptomatically directed. Opioid addiction is often comorbid with other addictions (e.g., to cocaine and alcohol). Currently, we are also investigating development of medications to treat cocaine addiction and alcoholism, with the κ-opioid receptor as one major potential target (*109*–*111*).

One current goal would be the discovery of targets and approaches that may prevent the onset of OUDs after relatively brief exposure to μ-agonists (e.g., after short-term iatrogenic exposure for analgesia), with the aim of preventing the development of severe OUDs.

Studies have also shown that persons with OUD show persistently changed neuroendocrine stress–axis systems, which may contribute to continued risk of relapse (*112*). Recent work also shows that pain exposure per se (e.g., neuropathic or inflammatory pain) can result in neurobiological changes that could also increase the susceptibility of the individual to OUDs or to psychiatric comorbidities, such as anxiety or depression (*113*, *114*).

Novel technologies such as RNA interference and CRISPR (for somatic, not germ cells) may be explored in the future, for prevention or therapeutic uses, both for analgesia and for the treatment of OUD. These approaches could include targeting of particular neuroanatomical areas and mechanisms that may underlie specific facets of analgesia and of OUD treatment. As with all "gene therapy"–based approaches for CNS disorders, the development of vectors that can be expressed in a human relatively noninvasively and effectively will be crucial, as it is the avoidance of "off-target" effects (*115*).

## SUMMARY AND CONCLUSIONS

OUDs, including their most severe form, opioid addiction, are chronic relapsing diseases of the brain with multifactorial origins. Standard-of-care maintenance medications (methadone and buprenorphine-naloxone) are effective for the treatment of these diseases. However, the appropriate therapeutic use of these medications has been limited by stigma, insufficient medical education, and lack of resources. Ongoing research includes development of novel analgesic approaches that have greater effectiveness for chronic pain states (e.g., neuropathic and inflammatory pain), with a decreased burden of overdose risk and of abuse potential. Other approaches may also focus on mitigating the development of opioid addiction, before the emergence of substantial neurobiological changes and compulsive-like drug-taking behaviors.

## SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/5/10/eaax9140/DC1

Table S1. Methadone maintenance treatment for opiate (heroin) addiction.

Table S2. SNPs of genes related to endocrine stress responsivity that has been found to be associated with opioid addiction (*101*, *102*, *116*).

Fig. S1. Model for the contribution of pain states and pain treatment to the development of OUD.

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Original Investigation | Substance Use and Addiction

# Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder

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## Abstract

**IMPORTANCE** Although clinical trials demonstrate the superior effectiveness of medication for opioid use disorder (MOUD) compared with nonpharmacologic treatment, national data on the comparative effectiveness of real-world treatment pathways are lacking.

**OBJECTIVE** To examine associations between opioid use disorder (OUD) treatment pathways and overdose and opioid-related acute care use as proxies for OUD recurrence.

**DESIGN, SETTING, AND PARTICIPANTS** This retrospective comparative effectiveness research study assessed deidentified claims from the OptumLabs Data Warehouse from individuals aged 16 years or older with OUD and commercial or Medicare Advantage coverage. Opioid use disorder was identified based on 1 or more inpatient or 2 or more outpatient claims for OUD diagnosis codes within 3 months of each other; 1 or more claims for OUD plus diagnosis codes for opioid-related overdose, injection-related infection, or inpatient detoxification or residential services; or MOUD claims between January 1, 2015, and September 30, 2017. Data analysis was performed from April 1, 2018, to June 30, 2019.

**EXPOSURES** One of 6 mutually exclusive treatment pathways, including (1) no treatment, (2) inpatient detoxification or residential services, (3) intensive behavioral health, (4) buprenorphine or methadone, (5) naltrexone, and (6) nonintensive behavioral health.

**MAIN OUTCOMES AND MEASURES** Opioid-related overdose or serious acute care use during 3 and 12 months after initial treatment.

**RESULTS** A total of 40 885 individuals with OUD (mean [SD] age, 47.73 [17.25] years; 22 172 [54.2%] male; 30 332 [74.2%] white) were identified. For OUD treatment, 24 258 (59.3%) received nonintensive behavioral health, 6455 (15.8%) received inpatient detoxification or residential services, 5123 (12.5%) received MOUD treatment with buprenorphine or methadone, 1970 (4.8%) received intensive behavioral health, and 963 (2.4%) received MOUD treatment with naltrexone. During 3-month follow-up, 707 participants (1.7%) experienced an overdose, and 773 (1.9%) had serious opioid-related acute care use. Only treatment with buprenorphine or methadone was associated with a reduced risk of overdose during 3-month (adjusted hazard ratio [AHR], 0.24; 95% CI, 0.14-0.41) and 12-month (AHR, 0.41; 95% CI, 0.31-0.55) follow-up. Treatment with buprenorphine or methadone was also associated with reduction in serious opioid-related acute care use during 3-month (AHR, 0.68; 95% CI, 0.47-0.99) and 12-month (AHR, 0.74; 95% CI, 0.58-0.95) follow-up.

*(continued)*

### Key Points

**Question** What is the real-world effectiveness of different treatment pathways for opioid use disorder?

**Findings** In this comparative effectiveness research study of 40 885 adults with opioid use disorder that compared 6 different treatment pathways, only treatment with buprenorphine or methadone was associated with reduced risk of overdose and serious opioid-related acute care use compared with no treatment during 3 and 12 months of follow-up.

**Meaning** Methadone and buprenorphine were associated with reduced overdose and opioid-related morbidity compared with opioid antagonist therapy, inpatient treatment, or intensive outpatient behavioral interventions and may be used as first-line treatments for opioid use disorder.

**+ Supplemental content**

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*Abstract (continued)*

**CONCLUSIONS AND RELEVANCE** Treatment with buprenorphine or methadone was associated with reductions in overdose and serious opioid-related acute care use compared with other treatments. Strategies to address the underuse of MOUD are needed.

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## Introduction

The increasing burden of opioid use disorder (OUD) has resulted in increased opioid-related morbidity and mortality, with 47 600 overdose deaths in 2017 alone.[1-3] From 2002 to 2012, hospitalization costs attributable to opioid-related overdose increased by more than $700 million annually.[4] Associated health complications, such as hepatitis C infection, HIV infection, and serious injection-related infections, are also increasing.[5-7] In addition, as rates of opioid-related death have increased despite decreases in prescription opioid supply, there is an increasing recognition that greater attention must be paid to improving access to effective OUD treatment.[8,9]

Medication for opioid use disorder (MOUD) is effective and improves mortality, treatment retention, and remission, but most people with OUD remain untreated.[10-15] Many parts of the United States lack access to buprenorphine prescribers, and only a few addiction treatment programs offer all forms of MOUD.[16-18] This lack of access has resulted in a treatment gap of an estimated 1 million people with OUD untreated with MOUD annually.[19]

Nationally representative, comparative effectiveness studies of MOUD compared with nonpharmacologic treatment are limited. One prior study[12] compared MOUD with psychosocial treatments but was limited to a Massachusetts Medicaid population. Studies[20-23] examining OUD treatment among nationally representative populations have examined trends in MOUD initiation, patterns of OUD treatment, and effectiveness of different types of MOUD at reducing overdose using Medicaid and commercial claims data. However, none of those studies[20-23] compared the effectiveness of MOUD with nonpharmacologic treatments in a national sample. Despite better access to medical care, only a few commercially insured patients are treated with MOUD, and psychosocial-only treatments continue to be common, suggesting that greater understanding of the comparative effectiveness of these different treatments is needed.[21]

In this study, we used a large, nationally representative database of commercially insured and Medicare Advantage (MA) individuals to evaluate the effectiveness of MOUD compared with nonpharmacologic treatment. This retrospective comparative effectiveness study was designed to inform treatment decisions made by policy makers, insurers, practitioners, and patients.

## Methods

We conducted a comparative effectiveness research study using the OptumLabs Data Warehouse, which includes medical, behavioral health, and pharmacy claims for commercial and MA enrollees.[24] The database represents a diverse mixture of ages, races/ethnicities, and geographic regions across the United States. Our analysis used deidentified administrative claims data. The window for identification of OUD for this study was January 1, 2015, to September 30, 2017. The study used claims data from October 3, 2014, to December 31, 2017, to allow for a 90-day period to ensure a nonopioid clean period and a minimum of 90 days of follow-up for all individuals with diagnosed OUD. Data analysis was performed from April 1, 2018, to June 30, 2019. Because this study involved analysis of preexisting, deidentified data, the Chesapeake Institutional Review Board deemed it exempt from institutional review board approval. This study followed the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) reporting guideline.[25]

### Cohort Selection

We defined OUD as 1 or more inpatient or 2 or more outpatient claims for *International Classification of Diseases, Ninth Revision (ICD-9)* or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* diagnosis codes for opioid dependence that occurred within 3 months of each other; 1 or more claims for diagnosis codes for opioid dependence, opioid use, or opioid abuse plus diagnosis codes for an encounter related to opioid overdose or an injection-related infection, opioid-related inpatient detoxification or residential services; or claims for MOUD or detoxification (eFigure 1 in the Supplement). Cohort inclusion required presence of OUD and age of 16 years or older; commercial or MA medical, pharmacy, and behavioral coverage; and continuous enrollment for 3 months before and after OUD treatment initiation date. For those in the no treatment group, a treatment initiation index date was selected at random that matched the treated groups (eAppendix 1 in the Supplement).

### Treatment Pathways

We examined treatments received in the 3 months after OUD diagnosis during the first 90 days after cohort entry to identify patterns of treatment (eFigure 2 in the Supplement). We categorized individuals into 1 of 6 mutually exclusive pathway designations based on initial treatment: (1) no treatment, (2) inpatient detoxification or residential services, (3) intensive behavioral health (intensive outpatient or partial hospitalization), (4) buprenorphine or methadone, (5) naltrexone, and (6) only nonintensive behavioral health (outpatient counseling) (eAppendix 2 in the Supplement). In addition, we examined mean duration of MOUD treatment in days.

Classification of treatment pathways was informed by detailed exploration of the sequence of treatment modalities provided to patients using medical and pharmacy claims (eFigure 3 in the Supplement). For this study, consistent with an intent-to-treat design, patients were assigned to the initial treatment received.

### Outcomes

Our primary outcomes were overdose or serious opioid-related acute care use, defined as an emergency department or hospitalization with a primary opioid diagnosis code. Overdose was identified based on diagnosis codes from claims for health care encounters. These encounters may include both fatal and nonfatal overdose (lack of mortality data preclude that determination). For actively treated individuals, the index date was the date of first treatment. For untreated individuals, the index date was set randomly based on the distribution of time to first treatment among actively treated individuals. Risk for adverse outcomes started 1 day after the index date; however, because the time sequence for adverse events that occurred during an initial inpatient treatment could not be reliably established, risk of adverse outcomes started 1 day after inpatient discharge. Time to event was calculated as (event date − index date + 1), which is consistent with an intent-to-treat analysis for all treatment pathways. Individuals were censored at the earlier outcome, health plan disenrollment, or 12 months. We selected overdose and opioid-related acute care use as negative clinical outcomes, which likely indicate recurrence of OUD. These outcomes may underestimate the prevalence of OUD recurrence because they represent severe consequences of ongoing use.

A secondary outcome was admission to inpatient detoxification or readmission for those who initiated treatment with inpatient detoxification or residential services. All outcomes were evaluated for 3 months and 12 months after treatment initiation. In the absence of an event, patients were followed up until the earliest date of health plan disenrollment or end of the respective period.

### Statistical Analysis

We used Cox proportional hazards regression models to estimate the hazard ratios (HRs) for primary and secondary outcomes, adjusting for age, sex, race/ethnicity, insurance type, baseline cost rank, mental health and medical comorbidities, and injection-related infections or overdose at study inclusion. For medical comorbidities, we used a modified Elixhauser index that excluded mental

health subcomponents because they were classified separately.[26] All analyses were conducted using an intent-to-treat approach that attributed patient outcomes to their initial treatment category. We conducted a subanalysis of patients who received methadone or buprenorphine, stratifying by duration of MOUD treatment as 1 to 30 days, 31 to 180 days, or more than 180 days.

For the secondary outcome of admission to inpatient detoxification, we conducted a subanalysis in which patients in the no treatment and nonintensive behavioral health groups were removed from the sample. These 2 treatment pathways were, by definition, required to not have any treatment (no treatment group) or any treatment other than outpatient behavioral health treatment (nonintensive behavioral health group) in the first 3 months of follow-up, which made them systematically different from the other pathways evaluated for this outcome.

Analysis of survival for all outcomes was performed using unadjusted Kaplan-Meier curves and adjusted Cox proportional hazards regression (PHREG procedure, SAS Enterprise Guide, version 7.13 [SAS Institute Inc]) under both 3-month and 12-month time windows to examine potential survivorship bias and informative censoring. For the unadjusted analysis, the log-rank test is reported; 95% Wald CIs are reported for the adjusted HRs (AHRs). The proportionality assumption was assessed visually and tested by including treatment pathway as a time-dependent covariate in the Cox proportional hazards regression model. Hazards appeared to be proportional during 3 months, but there was evidence of nonproportionality for the behavioral health outpatient pathway during the 12-month time window.

## Results

### Cohort Characteristics

A total of 40 885 individuals with OUD (mean [SD] age, 47.73 [17.25] years; 22 172 [54.2%] male; 30 332 [74.2%] white) were identified. A total of 23 636 (57.8%) were commercially insured, and 17 249 (42.2%) were enrolled in MA plans. Of those with MA, 10 322 (25.2%) were younger than 65 years. Non–substance use disorder mental health comorbidities in the 3 months before the index date were found in 10 942 individuals (45.1%) in the cohort. Depression (9733 [23.8%]) and anxiety (10 704 [26.2%]) were most common (**Table 1**).

The most common treatment pathway was nonintensive behavioral health (24 258 [59.3%]), followed by inpatient detoxification or residential services (6455 [15.8%]) and buprenorphine or methadone (5123 [12.5%]). Not receiving any treatment was more common (2116 [5.2%]) than naltrexone (963 [2.4%]) or intensive behavioral health (1970 [4.8%]). Mean (SD) length of stay in inpatient detoxification or residential services was 7.47 (10.35) days. For the 5048 in that group who had at least 6 months of continuous enrollment, mean (SD) length of stay was 7.56 (10.99) days. For the 3098 in that group who had at least 12 months of continuous enrollment, mean (SD) length of stay was 7.64 (12.24) days.

Maintaining continuous commercial health insurance was challenging in this cohort; 19 685 (48.1%) were disenrolled by 12 months after the index date. Individuals receiving nonintensive behavioral health had the lowest disenrollment (11 037 [45.5%]), and those receiving MOUD treatment with buprenorphine or methadone (2755 [53.8%]) and MOUD treatment with naltrexone (520 [54.0%]) had the highest disenrollment rates. No differences were found between those who maintained enrollment and those who were disenrolled with regard to race/ethnicity, comorbidities, or markers of severity of OUD, including those with a history of an injection-related infection, hepatitis C infection, or overdose. It was not possible to distinguish disenrollment attributable to death from disenrollment for other reasons (eg, health insurance options offered by employers). Details on demographic characteristics and comorbidities by treatment group for individuals who were disenrolled are provided in the eTable in the Supplement.

## Recurrence Outcomes

During the 3-month follow-up period, 707 participants (1.7%) experienced an overdose, and 773 (1.9%) had a serious opioid-related acute care use episode. Only individuals receiving MOUD treatment with buprenorphine or methadone were less likely to experience an overdose compared with those receiving no treatment (AHR, 0.24; 95% CI, 0.14-0.41) (**Table 2** and **Figure 1**A). Inpatient detoxification or residential services (AHR, 0.82; 95% CI, 0.57-1.19), naltrexone (AHR, 0.59; 95% CI, 0.29-1.20), nonintensive behavioral health services (AHR, 0.92; 95% CI, 0.67-1.27), or intensive

**Table 1. Patient Characteristics[a]**

| Characteristic | Total | No Treatment | Inpatient Detoxification or Residential Services | BH IOP | MOUD | | BH Other |
|---|---|---|---|---|---|---|---|
| | | | | | Buprenorphine or Methadone | Naltrexone | |
| Total sample | 40 885 (100) | 2116 (5.2) | 6455 (15.8) | 1970 (4.8) | 5123 (12.5) | 963 (2.4) | 24 258 (59.3) |
| Age, mean (SD), y | 47.73 (17.25) | 44.85 (18.66) | 39.22 (15.38) | 31.28 (12.19) | 42.58 (13.93) | 38.10 (14.01) | 53.05 (16.36) |
| Follow-up duration, mean (SD), d | 293.2 (91.3) | 285.0 (93.9) | 284.3 (96.1) | 291.1 (93.2) | 281.8 (94.7) | 282.5 (94.5) | 299.3 (88.1) |
| Age group, y | | | | | | | |
| 16-25 | 5978 (14.6) | 437 (20.7) | 1837 (28.5) | 948 (48.1) | 578 (11.3) | 247 (25.6) | 1931 (8.0) |
| 26-34 | 5350 (13.1) | 354 (16.7) | 1124 (17.4) | 404 (20.5) | 1194 (23.3) | 197 (20.5) | 2077 (8.6) |
| 35-44 | 6070 (14.8) | 332 (15.7) | 1089 (16.9) | 290 (14.7) | 1172 (22.9) | 206 (21.4) | 2981 (12.3) |
| 45-54 | 7208 (17.6) | 300 (14.2) | 1059 (16.4) | 188 (9.5) | 995 (19.4) | 167 (17.3) | 4499 (18.5) |
| 54-64 | 8897 (21.8) | 318 (15.0) | 983 (15.2) | 117 (5.9) | 817 (15.9) | 108 (11.2) | 6554 (27) |
| ≥65 | 7382 (18.1) | 375 (17.7) | 363 (5.6) | 23 (1.2) | 367 (7.2) | 38 (3.9) | 6216 (25.6) |
| Sex | | | | | | | |
| Female | 18 713 (45.8) | 797 (37.7) | 2482 (38.5) | 662 (33.6) | 1971 (38.5) | 387 (40.2) | 12 414 (51.2) |
| Male | 22 172 (54.2) | 1319 (62.3) | 3973 (61.5) | 1308 (66.4) | 3152 (61.5) | 576 (59.8) | 11 844 (48.8) |
| Insurance type | | | | | | | |
| Commercial | 23 636 (57.8) | 1299 (61.4) | 5062 (78.4) | 1889 (95.9) | 3630 (70.9) | 841 (87.3) | 10 915 (45) |
| Medicare Advantage | | | | | | | |
| Age <65 y | 10 322 (25.2) | 457 (21.6) | 1067 (16.5) | 63 (3.2) | 1147 (22.4) | 91 (9.4) | 7497 (30.9) |
| Age ≥65 y | 6927 (16.9) | 360 (17.0) | 326 (5.1) | 18 (0.9) | 346 (6.8) | 31 (3.2) | 5846 (24.1) |
| Race/ethnicity | | | | | | | |
| White | 30 332 (74.2) | 1485 (70.2) | 4976 (16.4) | 1552 (78.8) | 4044 (78.9) | 791 (82.1) | 17 484 (72.1) |
| Hispanic | 3388 (8.3) | 192 (9.1) | 511 (15.1) | 158 (8.0) | 338 (6.6) | 47 (4.9) | 2142 (8.8) |
| Black | 4991 (12.2) | 317 (15.0) | 628 (12.6) | 161 (8.2) | 468 (9.1) | 68 (7.1) | 3349 (13.8) |
| Other or unknown | 2174 (5.3) | 122 (5.8) | 340 (15.6) | 99 (5.0) | 273 (5.3) | 57 (5.9) | 1283 (5.3) |
| Elixhauser index score excluding mental health, mean (SD) | 1.75 (2.35) | 1.25 (2.15) | 1.00 (1.67) | 0.51 (1.15) | 0.88 (1.49) | 0.94 (1.41) | 2.30 (2.60) |
| Any mental health diagnosis | 18 218 (44.6) | 585 (27.6) | 3078 (47.7) | 933 (47.4) | 2060 (40.2) | 620 (64.4) | 10 942 (45.1) |
| Depression | 9733 (23.8) | 270 (12.8) | 1670 (25.9) | 552 (28.0) | 965 (18.8) | 398 (41.3) | 5878 (24.2) |
| Anxiety | 10 704 (26.2) | 274 (12.9) | 1921 (29.8) | 554 (28.1) | 1329 (25.9) | 391 (40.6) | 6235 (25.7) |
| ADHD | 1774 (4.3) | 33 (1.6) | 402 (6.2) | 159 (8.1) | 272 (5.3) | 77 (8.0) | 831 (3.4) |
| PTSD | 1462 (3.6) | 41 (1.9) | 245 (3.8) | 104 (5.3) | 153 (3.0) | 69 (7.2) | 850 (3.5) |
| Alcohol | 4166 (10.2) | 174 (8.2) | 961 (14.9) | 471 (23.9) | 225 (4.4) | 496 (51.5) | 1839 (7.6) |
| Bipolar disorder | 3138 (7.7) | 102 (4.8) | 556 (8.6) | 183 (9.3) | 290 (5.7) | 146 (15.2) | 1861 (7.7) |
| Psychosis | 1526 (3.7) | 76 (3.6) | 268 (4.2) | 76 (3.9) | 87 (1.7) | 40 (4.2) | 979 (4) |
| IDU infection | 5556 (13.6) | 249 (11.8) | 330 (5.1) | 66 (3.4) | 151 (2.9) | 31 (3.2) | 4729 (19.5) |
| Hepatitis C | 2018 (4.9) | 64 (3.0) | 181 (2.8) | <29 (<1.7) | 121 (2.4) | <11 (<1.1) | 1623 (6.7) |
| Opioid overdose | 2135 (5.2) | 249 (11.8) | 267 (4.1) | 84 (4.3) | 86 (1.7) | 27 (2.8) | 1422 (5.9) |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BH IOP, intensive behavioral health (intensive outpatient or partial hospitalization); BH other, only nonintensive behavioral health (outpatient counseling); IDU, injection drug use; MOUD, medication for opioid use disorder; PTSD, posttraumatic stress disorder.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

behavioral health services (AHR, 0.81; 95% CI, 0.50-1.32) were not significantly associated with overdose.

MOUD treatment with buprenorphine or methadone was also protective against serious opioid-related acute care use during the 3-month follow-up period (AHR, 0.68; 95% CI, 0.47-0.99) (Table 2 and Figure 1B). Inpatient detoxification or residential services treatment, naltrexone, and intensive behavioral health services were not significantly associated with serious opioid-related acute care use during 3 months (inpatient detoxification or residential services: AHR, 1.05; 95% CI, 0.76-1.45; naltrexone: AHR, 1.15; 95% CI, 0.69-1.92; intensive behavioral health: AHR, 0.84; 95% CI, 0.54-1.30).

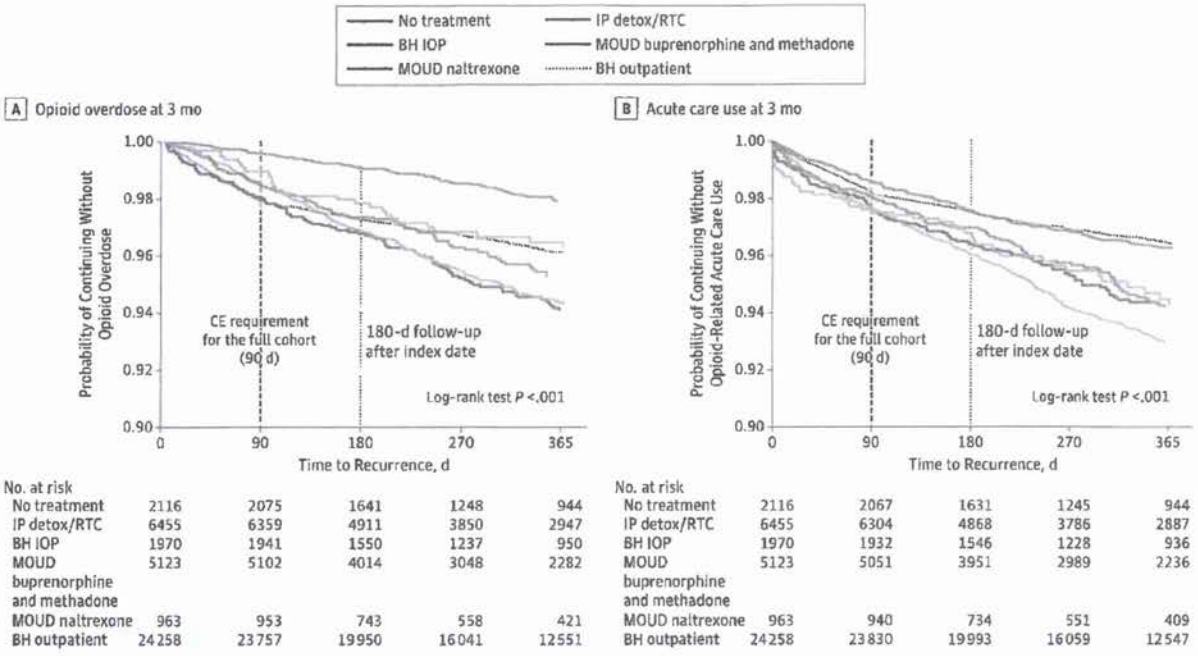
**Table 2. Adjusted Hazard Ratios for Overdose and Serious Opioid-Related Acute Care Use by Initial Treatment Group Compared With No Treatment[a]**

| Variable | Adjusted Hazard Ratio (95% CI) | |
|---|---|---|
| | 3 Months | 12 Months |
| Overdose | | |
| No treatment | 1 [Reference] | 1 [Reference] |
| Inpatient detoxification or residential services | 0.82 (0.57-1.19) | 1 (0.79-1.25) |
| BH IOP | 0.81 (0.50-1.32) | 0.75 (0.56-1.02) |
| MOUD treatment with buprenorphine or methadone | 0.24 (0.14-0.41) | 0.41 (0.31-0.55) |
| MOUD treatment with naltrexone | 0.59 (0.29-1.20) | 0.73 (0.48-1.11) |
| BH other | 0.92 (0.67-1.27) | 0.69 (0.56-0.85) |
| ED or inpatient stay | | |
| No treatment | 1 [Reference] | 1 [Reference] |
| Inpatient detoxification or residential services | 1.05 (0.76-1.45) | 1.20 (0.96-1.50) |
| BH IOP | 0.84 (0.54-1.30) | 0 90 (0.67-1.20) |
| MOUD treatment with buprenorphine or methadone | 0.68 (0.47-0.99) | 0.74 (0.58-0.95) |
| MOUD treatment with naltrexone | 1.15 (0.69-1.92) | 1.07 (0.75-1.54) |
| BH other | 0.59 (0.44-0.80) | 0.60 (0.48-0.74) |

Abbreviations: BH IOP, intensive behavioral health (intensive outpatient or partial hospitalization); BH other, only nonintensive behavioral health (outpatient counseling); ED, emergency department; MOUD, medication for opioid use disorder.

[a] The hazard ratios were adjusted for age, sex, race/ethnicity, insurance type, baseline medical (modified Elixhauser index score) and mental health comorbidities (depression, anxiety, posttraumatic stress disorder, and attention-deficit/hyperactivity disorder), evidence of overdose or infections related to intravenous drug use, and cost rank.

**Figure 1. Probability of Opioid Overdose and Acute Care Use During the 3-Month Follow-up Period**




BH indicates behavioral health; CE, continuing education; BH IOP, intensive behavioral health (intensive outpatient or partial hospitalization); IP detox/RTC, inpatient detoxification or residential services; and MOUD, medication for opioid use disorder.

Nonintensive behavioral health services were associated with a reduction in serious opioid-related acute care use (AHR, 0.59; 95% CI, 0.44-0.80). Receiving MOUD treatment with buprenorphine or methadone continued to be protective against overdose (AHR, 0.41; 95% CI, 0.31-0.55) and serious opioid-related acute care use (AHR, 0.74; 95% CI, 0.58-0.95) at 12 months.

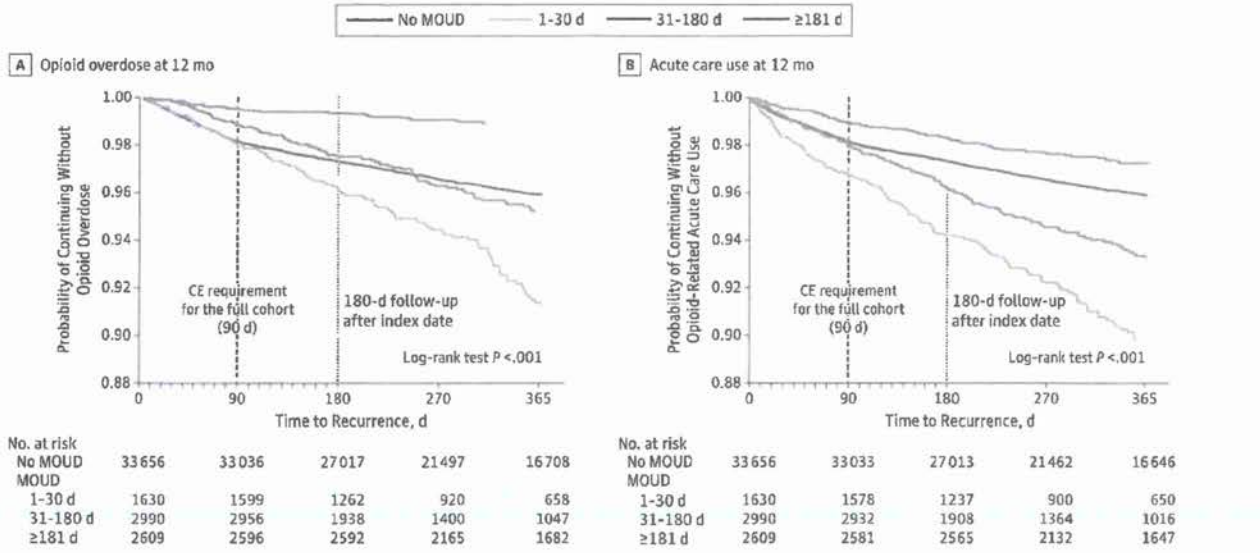
Compared with MOUD treatment with buprenorphine or methadone, all treatment groups were more likely to have a posttreatment admission to inpatient detoxification. Patients who initiated treatment with inpatient detoxification or residential services were most likely to return within 3 months (AHR, 3.76; 95% CI, 2.98-4.74) and 12 months (AHR, 3.48; 95% CI, 3.02-4.01). However, treatment with naltrexone or intensive behavioral health services was also associated with a higher risk of subsequent detoxification admission during the 3-month (naltrexone: AHR, 2.64; 95% CI, 1.84-3.78; intensive behavioral health: AHR, 2.19; 95% CI, 1.63-2.96) and 12-month (naltrexone: AHR, 1.98; 95% CI, 1.55-2.52; intensive behavioral health: AHR, 2.08; 95% CI, 1.73-2.50) follow-up periods.

### MOUD Treatment Duration

Treatment duration for MOUD was relatively short. During 12 months, the mean (SD) treatment duration for naltrexone was 74.41 (70.15) days and 149.65 (119.37) days for buprenorphine or methadone. Individuals who received longer-duration MOUD treatment with buprenorphine or methadone had lower rates of overdose (**Figure 2**A) or serious opioid-related acute care use (Figure 2B).

At the end of 12 months, 1198 (3.6%) of those who received no MOUD had an overdose, and 1204 (3.6%) had serious opioid-related acute care use; 105 (6.4%) of those who received MOUD treatment with buprenorphine or methadone for 1 to 30 days had an overdose, and 133 (8.2%) had serious opioid-related acute care use; 101 (3.4%) of those who received MOUD treatment with buprenorphine or methadone for 31 to 180 days had an overdose, and 148 (5.0%) had serious opioid-related acute care use; and 28 (1.1%) of those who received MOUD treatment with buprenorphine or methadone for more than 180 days had an overdose, and 69 (2.6%) had serious opioid-related acute care use.

**Figure 2. Probability of Opioid Overdose and Acute Care Use During the 12-Month Follow-up Period**




CE indicates continuing education; MOUD, medication for opioid use disorder.

## Discussion

In a national cohort of 40 885 insured individuals between 2015 and 2017, MOUD treatment with buprenorphine or methadone was associated with a 76% reduction in overdose at 3 months and a 59% reduction in overdose at 12 months. To our knowledge, this was the largest cohort of commercially insured or MA individuals with OUD studied in a real-world environment with complete medical, pharmacy, and behavioral health administrative claims.

Treatment with buprenorphine or methadone was associated with a 32% relative rate of reduction in serious opioid-related acute care use at 3 months and a 26% relative rate of reduction at 12 months compared with no treatment. In contrast, detoxification, intensive behavioral health, and naltrexone treatment were not associated with reduced overdose or serious opioid-related acute care use at 3 or 12 months.

Despite the known benefit of MOUD treatment with buprenorphine or methadone, only 12.5% initiated these evidence-based treatments. Most individuals in this cohort initiated treatment with psychosocial services alone or inpatient detoxification, both of which are less effective than MOUD. It is possible that individuals accessed public sector treatments that were not captured in our data, particularly for methadone, which was not covered by Medicare and may not have been covered without co-payment for all commercial plans during this time. Low rates of MOUD use among an insured population highlight the need for strategies to improve access to and coverage for MOUD treatment.

Our results demonstrate the importance of treatment retention with MOUD. Individuals who received methadone or buprenorphine for longer than 6 months experienced fewer overdose events and serious opioid-related acute care use compared with those who received shorter durations of treatment or no treatment. These findings are consistent with prior research[11,15,27-29] demonstrating high rates of recurrent opioid use if MOUD treatment is discontinued prematurely. Despite the benefit of MOUD in our study, treatment duration was relatively short. Given the chronic nature of OUD and the evidence that longer treatment duration may be associated with improved outcomes, patient-centered MOUD treatment models explicitly focused on engagement and retention are needed. Low-threshold treatment, which aims to reduce barriers to entry and is tailored to the needs of high-risk populations,[30] may be a strategy to improve retention; however, to our knowledge, no rigorous studies have evaluated these models to date.[31,32] In addition, patient-centered MOUD care, which allows participants to determine the services they need rather than requirements, such as mandatory counseling, are noninferior to traditional treatment.[32]

Numerous barriers limit sustained engagement in MOUD, including a lack of access to waivered practitioners, high co-payments, prior authorization requirements, and other restrictions on use. Previous studies[33,34] have demonstrated that restrictions on use for MOUD are associated with limited access and harm. Addiction treatment programs in states that require Medicaid prior authorizations for buprenorphine are less likely to offer buprenorphine, and the more restrictions on use in state Medicaid programs, the fewer treatment programs that offer buprenorphine.[33] Requiring prior authorization for higher doses of buprenorphine may also result in increased recurrence rates among patients.[34] Our finding that MOUD treatment with buprenorphine or methadone was associated with lower overdose and serious opioid-related acute care use supports expanded coverage of these medications without restrictions on use.

Our findings are also consistent with analyses showing that MOUD treatment with buprenorphine or methadone is significantly associated with reduced overdose and recurrence of opioid use compared with no treatment or non-MOUD treatment. A previous cohort study[15] of individuals in Massachusetts demonstrated a reduction in overdose-related mortality associated with treatment with buprenorphine (AHR, 0.62; 95% CI, 0.41-0.92) or methadone (AHR, 0.41; 95% CI, 0.24-0.70), results that are similar to our finding of an AHR of 0.41 (95% CI, 0.31-0.55) for overdose at 12 months for methadone or buprenorphine. A large meta-analysis[11] examining mortality when individuals were in or out of treatment with buprenorphine or methadone similarly showed

decreased overdose mortality during treatment. A study[12] examining proxies for recurrent OUD among Massachusetts Medicaid enrollees found that treatment with buprenorphine or methadone was associated with lower recurrence rates and costs. No studies, to our knowledge, have examined the effect of different OUD treatment pathways on overdose and serious opioid-related acute care use among a national sample of commercially insured and MA enrollees.

Our finding that MOUD treatment with naltrexone was not protective against overdose or serious opioid-related acute care use is consistent with other studies[15,35] that found naltrexone to be less effective than MOUD treatment with buprenorphine. The mean (SD) treatment duration for naltrexone in this cohort was longer than prior observational studies at 74.41 (70.15) days.

The findings that nonintensive behavioral health treatment was associated with a reduced risk of overdose at 12 months but not 3 months and a reduced risk of opioid-related acute care use was surprising. Although we attempted to control for differences among various treatment groups, individuals referred to nonintensive behavioral health may represent a less complex patient population than those who receive MOUD treatment or are referred to intensive behavioral health or inpatient treatment.

### Strengths and Limitations

Specifically, we identified a research question a priori that was meaningful, had clinical and policy implications, and was concise and unambiguous. Our study design's strengths are the large, nationally representative sample and complete claims data, which allowed us to adequately identify appropriate patients and interventions. In addition, we used a conservative definition of OUD and of proxies for OUD recurrence to limit inclusion of individuals who did not have OUD or of outcomes that did not represent clinically significant recurrence.

This study has limitations. The limitations of our study design include the lack of clinical information in claims data or outcomes that occurred outside a health care encounter (eg, fatal overdoses or active use without medical complication). As with any observational study, there is the possibility that unmeasured patient characteristics were associated with treatment assignment and outcomes, possibly biasing estimates of outcomes associated with MOUD treatment groups. It is also possible that individuals selected for different treatments differed by characteristics that were also associated with the outcomes. We were able to control for many patient characteristics, such as race/ethnicity, sex, insurance type, and comorbidities, but selection bias is possible. Another limitation is the degree of sample attrition during the 12-month follow-up period. However, we attempted to assess potential bias from informative censoring in 2 ways.[36] First, we compared the baseline characteristics of censored and uncensored cases. These distributions were similar, suggesting that, at least on the basis of observable characteristics, censored cases were not statistically different from uncensored cases. Second, we examined the proportionality of HRs. Visual inspection of the HRs indicated that they were proportional for the 3-month period but could not be assumed to be proportional for the 12-month period. Another limitation is the risk of immortal time bias by requiring 3-month enrollment for inclusion; however, we believed it was important to require 3 months of follow-up to adequately measure outcomes. In addition, assessment of community mortality with claims data is characterized by high degrees of measurement error. Traditional instrumental variable methods for addressing immortal time bias cannot be applied to survival models because of their nonlinear functional form.

## Conclusions

In a national sample of commercial insurance and MA enrollees with OUD, treatment with buprenorphine or methadone was associated with reductions in overdose and serious opioid-related acute care use, but only a few individuals were treated with these medications. These findings suggest that opportunities exist for health plans to reduce restrictions on use for MOUD and the need for treatment models that prioritize access to and retention of MOUD treatment.

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**Author Contributions:** Drs Wakeman and Sanghavi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Concept and design:* Wakeman, Larochelle, Ameli, Chaisson, Crown, Azocar, Sanghavi.

*Acquisition, analysis, or interpretation of data:* Wakeman, Larochelle, Ameli, Chaisson, McPheeters, Crown, Azocar.

*Drafting of the manuscript:* Wakeman, Ameli, Crown, Azocar.

*Critical revision of the manuscript for important intellectual content:* Wakeman, Larochelle, Ameli, Chaisson, McPheeters, Crown, Sanghavi.

*Statistical analysis:* Ameli, McPheeters, Crown.

*Administrative, technical, or material support:* Chaisson, McPheeters, Azocar.

*Supervision:* Chaisson, Sanghavi.

**Conflict of Interest Disclosures:** Dr Wakeman reported receiving personal fees from OptumLabs during the conduct of the study. Dr Ameli reported receiving grants from OptumLabs during the conduct of the study. Ms Chaisson, Mr McPheeters, and Dr Azocar reported receiving salary support from OptumLabs during the conduct of the study. Dr Azocar also reported receiving salary support from United Health Group outside the submitted work. Dr Sanghavi reported being an employee of United Health Group. No other disclosures were reported.

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**SUPPLEMENT.**

**eAppendix 1.** Cohort Selection
**eAppendix 2.** Supplementary Methods
**eFigure 1.** Definition of OUD
**eFigure 2.** Cohort Inclusion and Timeline
**eFigure 3.** Alluvial Flow of OUD Treatment Pathways in the Initial Cohort
**eTable.** Censoring by Baseline Characteristics

**From:** Harrell, Ashley <ashley.harrell@dmas.virginia.gov>
**Sent:** Tuesday, January 17, 2023 1:55 PM
**To:** Harp, William L. (DHP) <William.Harp@DHP.VIRGINIA.GOV>; Morton, Colanthia D. (DHP) <CoCo.Morton@dhp.virginia.gov>
**Cc:** Morgan, John (DMAS) <John.Morgan@dmas.virginia.gov>; Lowe, Jason (DMAS) <Jason.Lowe@dmas.virginia.gov>; Winn, Oketa (DMAS) <Oketa.Winn@dmas.virginia.gov>
**Subject:** Re: Board of Medicine Regulatory Advisory Panel (RAP)

Good afternoon,

We received this feedback from one of our MCOs and sharing:

Please see our recommendations below:

"When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids (recommendation category: A; evidence type: 4)." Current VA Treatment guidelines suggest the use of "short acting opioids" for the initiation of opioid treatment for acute pain only. Recommend, evaluate to apply this standard across the board to include "acute, subacute, and chronic pain".

"Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient". Current VA Treatment guidelines to do not specify the importance of maximizing the use of nonpharmacologic/nonopioid pharmacologic therapies as first line treatment for subacute and chronic pain.

"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 rapidly reduce opioid dosages from higher dosages (recommendation category: B; evidence type: 4)." "Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death". Recommend VA Treatment guidelines include these considerations under treatment of chronic opioid use disorder for patients evaluated to have an opioid use disorder.

Recommend adding "Liver Function Tests" at baseline for the "Patient assessment and Treatment Planning of addiction Treatment" for Buprenorphine Prescribing.

Thank you for the opportunity to share feedback.
Ashley

Dear Dr.:

Thank you for your question. I have consulted with BOM and BOP staff, and have confirmed that neither BOM nor BOP have a requirement in law or regulation for the prescriber to destroy medications before issuing a new prescription, so I cannot speak to the pharmacist's view that such must be confirmed before s/he could issue the prescription.

The DEA does not allow a patient to return a SII-V drug to the prescriber or pharmacist. The patient may only destroy it. An acceptable method of destruction is to place the drug in an appropriately identified collection receptacle which can often be found at police stations or some pharmacies. A list of pharmacies with receptacles can be found
here: https://www.dhp.virginia.gov/Pharmacy/destructionsites.asp
The patient may also bring the drugs for destruction to a community take-back event (you may search online or see advertised "Drug Take Back" days in your local community). The next one hosted by DEA is scheduled for April 22. https://www.deadiversion.usdoj.gov/drug_disposal/takeback/ As you note below, these receptable/take-back days will not issue what the pharmacist appears to believe is needed, so you may wish to direct the pharmacist to contact the BOP, as I have confirmed that this requirement is not reflective of BOP law/regulation.

I hope this information is helpful to you.

Kindest regards,

**Jennifer L. Deschenes, JD, MS**
**Deputy Executive Director, Discipline**
Virginia Board of Medicine

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**Subject:** Re: Medication Destruction - CFR Regs

Dear Ms. Deschenes,

Thank you for looking into this for us. In considering the problem, what seems to me to be an elegant solution has been offered by in that the "taken back for destruction" process becomes a supervised patient destruction event. This would mean that if a medication change is intended at an office visit (reasons being side effects, lack of efficacy, etc) so that a different medicine is to be prescribed, the patient would destroy the old medicines on site. The means of doing so would be the same (dissolving in water, adding coffee grounds, adding cat litter and then discarding the resulting aggregate) but our office would not receive the medicines from the patient. The process would take place at one of the nursing stations and would be witnessed by office staff with an attestation placed in the chart. As I read the CFR, end-user (patient) destruction is permitted but the regulations are mute on physicians being able to "take back" medicines. This is also what I understand your reply to state.

By making the end-user/patient the one who destroys the medicine, the same goal is realized, that of ensuring that the "old" medicines are not improperly used. This would be a danger if the old medicines were not definitively taken out of circulation, such as telling the patient to wait until the next fill date or by giving them medicines to counter withdrawal symptoms. Having the patient discard medicines at a disposal site does not ensure a strict accounting. To do so would need some sort of receipt from a disposal location, something that does not occur.

I do find it odd that there is virtually no available guidance about this problem. Perhaps the Board of Medicine could address the issue in any upcoming revisions of the Regulations Governing Prescribing of Opioids. I would be happy to help.

Thanks,

**From:** D. Bassam <dbassam@yahoo.com>
**Sent:** Friday, February 10, 2023 7:25 AM
**To:** Harp, William L. (DHP) <William.Harp@DHP.VIRGINIA.GOV>
**Cc:** Deschenes, Jennifer (DHP) <Jennifer.Deschenes@DHP.VIRGINIA.GOV>
**Subject:** Fw: Two items for your attention

Dear Dr. Harp,

I hope this email finds you and the rest of the staff at DHP doing well.

I was pleased to get this email regarding the plan to dispense with the x-waiver for the treatment of addiction.

I am hopeful that the repeal of the regulation will also include **18VAC85-21-150. Treatment with buprenorphine for addiction**

Currently there are significant restrictions to the prescribing of buprenorphine monoproduct (without naloxone) in the treatment of addiction. This creates barriers to use of buprenorphine that center on its cost to patients.

Pure buprenorphine (without naloxone) is already available for the treatment of pain (Butrans, Belbuca, generic buprenorphine patch).

Please consider the repeal or rewording of 18VAC85-21-150 to allow the prescription of buprenorphine monoproduct in the treatment of addiction. This would significantly lower the cost barrier and allow improved access to this life-saving drug for patients struggling with opiate addiction.

Sincerely,

Deeni Bassam, MD


The travel regulations require that "travelers must submit the Travel Expense Reimbursement Voucher **within 30 days after completion of their trip"**. (CAPP Topic 20335, State Travel Regulations, p.7). If you submit your reimbursement after the 30-day deadline, please provide a justification for the late submission and be aware that it may not be approved.

In order for the agency to be in compliance with the travel regulations, please submit your request for today's meeting no later than

**May 1, 2023**