Legislative Committee Meeting

Virginia Board of Medicine

January 19, 2018
8:30 a.m.

Legislative Committee

Virginia Board of Medicine
Friday, January 19, 2018, 8:30 a.m.
9960 Mayland Drive, Suite 200
Board Room 3
Henrico, VA 23233

Page

Call to Order – Ray Tuck, DC, Chair

Roll Call

Egress Instructions.....i

Approval of Minutes of May 19, 2017.....1-6

Adoption of Agenda

Public Comment on Agenda Items (15 minutes)

DHP Director Report.....---

Executive Director Report.....---

New Business

1. Report from the General Assembly – Elaine Yeatts – handout at meeting.....---
2. Chart of Regulatory Actions.....7-7
3. Review of Comments/Discussion of proposed regulations for opioid prescribing.....8-77
4. Reminder.....78

Announcements

Next Meeting: May 18, 2018

Adjournment

PERIMETER CENTER CONFERENCE CENTER
EMERGENCY EVACUATION OF BOARD AND TRAINING ROOMS
(Script to be read at the beginning of each meeting.)

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--- DRAFT UNAPPROVED --

VIRGINIA BOARD OF MEDICINE
LEGISLATIVE COMMITTEE MINUTES

Friday, May 19, 2017 Department of Health Professions Henrico, VA

CALL TO ORDER: The meeting convened at 8:31 a.m.

ROLL CALL: Mr. Heaberlin called the roll; a quorum was established.

MEMBERS PRESENT:
Kevin O'Connor, MD, Vice-President, Chair
Syed Salman Ali, MD
Wayne Reynolds, DO
Svinder Toor, MD
The Honorable Jasmine Gore

MEMBERS ABSENT
Barbara Allison-Bryan, MD, President
David Giammittorio, MD

STAFF PRESENT:
William L. Harp, MD, Executive Director
Jennifer Deschenes, JD, Deputy Director, Discipline
Alan Heaberlin, Deputy Director, Licensure
Barbara Matusiak, MD, Medical Review Coordinator
Colanthia Morton Opher, Operations Manager
David Brown, DC, DHP Director
Erin Barrett, JD, Assistant Attorney General

OTHERS PRESENT:
W. Scott Johnson, JD, HDJN & MSV
Ralston King, MSV
Carey Cox, VATAC
Sara Heisler, VHHA

EMERGENCY EGRESS INSTRUCTIONS

Dr. O'Connor provided the emergency egress instructions.

APPROVAL OF MINUTES of January 27, 2017

Dr. Ali moved to accept the meeting minutes as presented. The motion was seconded and carried.

ADOPTION OF AGENDA

Dr. Toor made a motion to accept the agenda as presented.

The motion was seconded and carried unanimously.

PUBLIC COMMENT

There was no public comment.

DHP DIRECTOR'S REPORT

Dr. Brown provided a brief report. He said that, in calendar year 2016, Virginia deaths related to opioid overdose were up 40% over calendar year 2015 and noted that there is no sign of this problem slowing. He commended the Regulatory Advisory Panel (RAP) for their work on the opioid regulations. He also noted that the workgroup of educators meeting next door with Dr. Hazel should be a great help in reducing opioid overdose death through prescriber education.

EXECUTIVE DIRECTOR'S REPORT

Dr. Harp did not have a report.

NEW BUSINESS

1. **Chart of Board of Medicine Regulatory Actions**

Elaine Yeatts provided a brief overview of this item. No action was required.

2. **Consideration of Recommendations from the Regulatory Advisory Panel, Supporting Documents, and Public Comment.**

Dr. O'Connor began by noting that he does not want to change the regulations based on anecdotal information.

Ms. Yeatts explained the different processes required to amend the emergency regulations and final regulations. The full Board in June will re-adopt the emergency regulations and move to adopt the full regulations to replace the emergency regulations upon their expiration. She then led the Committee through the recommendations from the RAP that met May 15, 2017.

18VAC85-21-70(C). After a brief discussion Dr. Ali moved to strike the first sentence of subsection C in the emergency regulations and to substitute the language, "Buprenorphine mono-product in tablet form shall not be prescribed for chronic pain." The motion was seconded and carried unanimously.

18VAC85-21-150(4). The Committee discussed how prescribers would be monitored to ensure they did not exceed 5% of patients being prescribed the mono-product. Dr. Harp, Dr. Brown and Ms. Deschenes all noted that the Prescription Monitoring Program (PMP) could be used to conduct prescriber audits. It was reported that Ralph Orr, PMP Director, could fashion a program to identify those that exceeded the established threshold.

Dr. Toor stated that he would like documentation on the patient's prescription that he/she is allergic to naloxone. He further asked for clarification on how the RAP chose 5% of patients as a threshold.

Dr. Harp stated that this number was agreed to by the RAP, which had believers and skeptics regarding naloxone intolerance. He stated that a member of the RAP noted his patients that were unable to tolerate the bi-product was around 5% of his total number of MAT patients.

Dr. Brown explained that having a clear percentage of patients in the regulations strengthens the hand of the Board. It will allow the PMP Advisory Panel to set the threshold for prescribers that are to be referred for investigation. A clear standard in the regulations will serve as a concrete basis for such referrals.

Dr. Ali asked Dr. Harp if the 5% number is necessary, and if it is his general belief that it is accurate that 5% of patients have problems with naloxone-containing product.

Dr. Harp stated that, according to the RAP, naloxone intolerance occurs in less than 5% of the patient population and that financial hardship is greater than 5%.

Dr. O'Connor stated that it is not the Board's purview to determine financial hardship. He favors reducing the 5% number to 3% and to strike "financial hardship" from the suggested revision. He further stated that a prescriber needs to have significant documentation in the medical record supporting why the mono-product is being prescribed.

Ms. Gore noted that she believed financial hardship should be included in the regulations. Financial hardship and the patient's ability to pay is a significant part of seeking and obtaining health care.

The Committee agreed that a 3% threshold would be enough to cover naloxone intolerance. Dr Toor made a motion to revise 18VAC85-21-150(4) to read, "For patients who have a demonstrated allergy or intolerance to naloxone, prescriptions for the mono-product shall not exceed 3% of the total prescriptions for buprenorphine written by the prescriber. Such exceptions must be clearly documented in the patient's medical record."

The motion was seconded and carried unanimously.

18VAC85-21-160(A).

Dr. Toor moved to change "shall" to "may." The motion was seconded and carried.

The Committee then began to review suggested edits to the final regulations that arose from the RAP's discussion.

18VAC85-21-10(2). The edit to include correctional facilities was discussed. Ms. Deschenes reviewed the reasons for including the revised language including correctional facilities, noting that the particular subsection dealt with acute and chronic pain, not addiction.

Dr. Ali noted that this particular population is already prone to drug-seeking behavior and exempting correctional facilities from the regulations is counterintuitive.

Ms. Deschenes said that patients in correctional facilities are administered the medication by a nurse who ensures that it is taken as prescribed.

Dr. Brown noted that the agency had not been contacted by any correctional facilities seeking such an exception.

By consensus, it was determined not to include the suggested revision in the final regulations.

18VAC85-21-30(B). A discussion was held regarding the feasibility of removing the specific Code language from this regulation.

Ms. Yeatts noted that striking the Code section language would require physicians to check the PMP if even one opioid tablet was prescribed.

The Committee agreed that this would result in an undue burden for physicians.

Dr. Brown told the Committee that the General Assembly had made it a standard to check the PMP when a prescription is written for a 7 day or greater supply of opioids.

By consensus, it was determined to leave this regulation as written.

180VAC85-21-40 & 18VAC85-21-70(5). Dr. Harp explained that the Board had gotten questions from pharmacists who have to call physicians in order to determine if the opioid prescriptions being written were legitimate, since allowable supplies differ for acute, surgical and chronic pain.

Dr. O'Connor stated that this recommendation appears to open an avenue for more complaints to the Board about physicians rather than improving patient care.

Dr. Brown noted that this particular revision is part of the final regulations which still must go out for another comment period. He noted that, without the proposed language, more calls will be made to prescribers by pharmacists who want to double-check why a prescription is being written.

Dr. Ali noted that this would be difficult to implement with physicians who write prescriptions electronically. It would be particularly difficult to document the type of pain on prescriptions generated in electronic medical records (EMR).

Dr. O'Connor said that this is not an issue about which people are complaining.

Dr. Toor moved not to include the revised language in the final regulations.

The motion was seconded and carried.

18VAC85-21-40(A)(C). This revision was requested because tramadol is an opioid and having it named separately in the regulation creates ambiguity. Dr. O'Connor said that there is no downside to leaving tramadol in the regulation as written, and by consensus it was decided tramadol would stay.

18VAC85-21-70(A)(3) & 18VAC85-21-80(C). After a brief discussion, Dr. Toor moved to strike "abuse" in the first regulation above and replace it with "misuse". He moved to strike the word "abuse" from the second regulation as well, replacing it with "misuse". The motion was seconded and carried.

3. **Draft Regulations for Licensure by Endorsement.**

Dr. Harp reviewed the "Draft Elements for Licensure by Endorsement" with the Committee.

Items under section 1 and 2 were agreed upon by consensus with no discussion.

Regarding section 3, a discussion was held on the period of practice a physician must attest to in order to be eligible for licensure by endorsement. Mr. Heaberlin suggested that, based upon his review of other states' regulations for licensure by endorsement, the Board should require 5 years of "continuous" or "active" practice defined as an average of 20 hours/week, or 640 hours a year.

Dr. Ali asked if residency and fellowships could be included in the 5 years of continuous or active practice.

Mr. Heaberlin noted that licensure by endorsement is intended to expedite licensure for physicians who have been practicing for several years and who already have a practice history. Physicians coming out of residency or fellowship are already expedited since there is less work history to be verified.

On section 4, Dr. Harp explained that North Carolina and other states that have licensure by endorsement accept the Canadian Board certifications as equivalent to the U.S. Board certifications.

For section 5, Dr. Harp explained the elements in a National Practitioner Data Bank report. The report includes medical malpractice payments, medical board history, licensure history and disciplinary actions taken by hospitals.

Dr. Ali noted the report was easy to obtain.

Dr. Harp asked if, since the NPDB report is so inclusive, would it be acceptable to the Board if only one license verification was required to document the 5 years of continuous licensure.

The Committee agreed that only one license verification would be needed. Dr. Toor also noted that the application should ask the applicant if he has ever resigned from a position or is under investigation by any other Board.

Dr. Toor moved to accept the "Draft Elements for Licensure by Endorsement" as reviewed by the Committee. The motion was seconded and carried unanimously.

ANNOUNCEMENTS

Please have your travel vouchers in by May 22nd.

The next Legislative Committee meeting will be September 8, 2017.

ADJOURNMENT

All business being completed, Dr. O'Connor adjourned the meeting at 10:07 a.m.

Kevin O'Connor, MD
Vice-President, Chair

William L. Harp, MD
Executive Director

Alan Heaberlin, Deputy Director, Licensing
Recording Secretary

Agenda Item: **Regulatory Actions - Chart of Regulatory Actions**

Staff Note: Attached is a chart with the status of regulations for the Board as of January 9, 2018

Board **Board of Medicine**

Chapter		Action / Stage Information
[18 VAC 85 - 20]	Regulations Governing the Practice of Medicine, Osteopathic Medicine, Podiatry, and Chiropractic	Licensure by endorsement [Action 4716] Proposed - *Register Date: 1/8/18* *Comment until 3/9/18* *Public hearing: 2/15/18*
[18 VAC 85 - 20]	Regulations Governing the Practice of Medicine, Osteopathic Medicine, Podiatry, and Chiropractic	Supervision and direction for laser hair removal [Action 4860] Proposed - *AT Attorney General's Office*
[18 VAC 85 - 20]	Regulations Governing the Practice of Medicine, Osteopathic Medicine, Podiatry, and Chiropractic	Renewal fee reduction [Action 4942] Final - *Register Date: 11/27/17* *Effective: 12/16/17*
[18 VAC 85 - 21]	Regulations Governing Prescribing of Opioids and Buprenorphine	Initial regulations [Action 4760] Proposed - *Register Date: 11/27/17* *Comment until 1/26/18*
[18 VAC 85 - 50]	Regulations Governing the Practice of Physician Assistants	Definitions of supervision and weight loss rules [Action 4943] NOIRA - *Register Date: 12/25/17* *Comment until 1/24/18*
[18 VAC 85 - 80]	Regulations for Licensure of Occupational Therapists	NBCOT certification as option for CE [Action 4461] Proposed - *Stage Withdrawn 6/28/2017* [Stage 7756]
[18 VAC 85 - 80]	Regulations for Licensure of Occupational Therapists	Elimination of CE form and change in title of regulation [Action 4849] Fast-Track - *Register Date: 10/30/17* *Effective: 12/14/17*
[18 VAC 85 - 130]	Regulations Governing the Practice of Licensed Midwives	Practical experience under supervision [Action 4944] Fast-Track - *At Governor's Office for 13 days*

Agenda Item: Review of Comments/Discussion of proposed regulations for opioid prescribing

Staff note:

The comment period on the proposed regulations for prescribing of opioids and buprenorphine ends on January 26, 2018. At the February board meeting, final regulations need to be adopted. The Legislative Committee is asked to review the comments to date and to consider what, if any, amendments should be suggested to the full board.

Enclosed are:

- A copy of proposed regulations
- Copy of comments
- Copy of CDC Guidelines

Committee Action:

No action is required; the comment period remains open

Proposed Text

Action: Initial regulations

Stage: Proposed

11/14/17 3:42 PM [latest]

18VAC85-21
CHAPTER 21

REGULATIONS GOVERNING PRESCRIBING OF OPIOIDS AND BUPRENORPHINE

18VAC85-21-10
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) a patient in hospice care, or (iii) 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.

18VAC85-21-20
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.

18VAC85-21-30
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.

18VAC85-21-40
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 pain shall 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 record the reasons to exceed 50 MME/day.

2. Prior to exceeding 120 MME/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. 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, 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 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.

18VAC85-21-50

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.

18VAC85-21-60
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.

18VAC85-21-70
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 record the reasons to exceed 50 MME/day;

2. Prior to exceeding 120 MME/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/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, 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.

18VAC85-21-80
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 medical record the presence or absence of any indicators for medication misuse or diversion and shall take appropriate action.

18VAC85-21-90
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.

18VAC85-21-100
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 at least every three months for the first year of treatment and at least every six months thereafter.

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.

18VAC85-21-110
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.

18VAC85-21-120
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.

18VAC85-21-130
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.

18VAC85-21-140
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.

18VAC85-21-150
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 containing naloxone 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, 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 if 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.

18VAC85-21-160
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, 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.

18VAC85-21-170
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.

STATEWIDE SICKLE CELL CHAPTERS OF VIRGINIA, INC.

POST OFFICE BOX 25205
RICHMOND, VIRGINIA 23260
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804-321-3350

Date: October 18, 2017

To: Members of the Boards of Medicine and the Medical Community
Elected and Government Officials
Federal and State Agencies
Sickle Cell Disease Association of America
Various Sickle Cell Organizations Nationwide

From: George Harris Carter, Administrator

Subject: Adverse Effects of the New Opioid Guidelines on Sickle Cell Patients

Sickle Cell Disease is an inherited blood disorder where normal soft round shaped red blood cells change to a hard sticky sickle or quarter-moon shape. This disease is produced when the sickle cell gene is transmitted by both parents to a child. Sickled shaped cells cannot squeeze through small blood vessels so they often jam up, blocking the flow of blood and oxygen to body parts and causing extreme pain. A pain crisis can last for days or even weeks and may occur several times a year. Lack of oxygen flow can also damage muscles, bones and internal organs and lead to strokes and other serious medical problems. There is no universal cure.

THE PAINFUL EPISODE OR SICKLE CELL CRISIS is the most common symptom suffered by those born with a Sickle Cell Disease. The patient experiences severe pain in chest, abdomen, back, arms, legs or hips. **Three times in my life I prayed to GOD to let me die because I could not stand the pain any longer.** Some patients live in pain on a daily basis. Pain undermines a person's physical, mental, and emotional well-being.

Statewide Sickle Cell Chapters of Virginia, Inc. (SSCCV), also known as Sickle Cell Chapters of Virginia or Statewide, a non-profit 501(c)(3) tax-exempt community-based organization, has a network of nine (9) community-based sickle cell disease organizations (chapters) that provide a variety of services across the Commonwealth. The chapters are located in Danville, Fredericksburg, Hampton, Lynchburg, Norfolk, Richmond, Rocky Mount, South Boston and Northern Virginia. Most of the chapters in this network have operated since 1972.

I am George Harris Carter and I'm 71 years old with Sickle Cell Disease. I serve as the Administrator (unpaid Executive Director) of Statewide Sickle Cell Chapters of Virginia. I want to voice concern about the potential negative effects the new CDC Opioid Guidelines are and will have on me and some or many of the **approximately 4,000 sickle cell patients around the State of Virginia and almost 96,000 in other parts of the United States.**

While illegal and excessive opioid use has increased overall, and something does need to be done about it, there is no evidence that this is true with patients who suffer with Sickle Cell Disease. Also, there is no evidence that doctors treating these patients are over prescribing opioids.

The new CDC Guidelines on Dose Limitation states the following:
"When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day. " (recommendation category: A, evidence type: 3)

The guidelines were meant to **SUGGEST** levels of MME above which prescribing **MAY** be unsafe. But some doctors may have taken the suggested MME levels as **ABSOLUTES**. Prescribing above 50 to 90 or more MME/day is now more likely to be viewed as deviating from or out of the standard-of-care. In some cases it may even be viewed as **CRIMINAL**.

At the end of the first paragraph on page 4 of the CDC Opioid Guidelines is the following statement:
"In addition, given the challenges of managing the painful complications of sickle cell disease, readers are referred to the NIH National Heart, Lung, and Blood Institute's Evidence Based Management of Sickle Cell Disease Expert Panel Report for management of sickle cell disease (46)."

The referenced document has **41** pages. Chapter 3 - Managing Acute Complications of Sickle Cell Disease (pages 14 through 17) and Chapter 4 - Managing Chronic Complications of Sickle Cell Disease (pages 27 and 28) discuss pain and opioids. These sections are not entitled "Pain Management" or so listed in the table of contents, so many doctors will not look further into the document, if they refer to it at all. The problem is the CDC guidelines discuss specific **numeric** doses while the NIH Report does not. The NIH Report is more of a discussion and outline of care with NO mention of minimal, average or high dosages. Numbers have a very specific meaning whereas words are open to discussion and interpretation.

With the introduction of the CDC dosage guidelines, a knowledgeable sickle cell doctor may be afraid to give opioids to sickle cell patients or may fear exceeding 50 MME/day because they are afraid of losing their medical license. But to the ones with little knowledge of sickle cell and/or those who view us as drug seekers, the new guidelines will give them more reason or justification to **undertreat** us or not give us any opioids. We may be facing a **backlash** because of the opioid crisis.

It took a long time to get many physicians to a point that they were willing to give higher doses and/or long-acting opioids to sickle cell patients. Unfortunately, the new opioid guidelines are undoing much of the work we previously accomplished. The guidelines have had an impact on some physicians' attitudes about prescribing opioids for pain and as a result, **unintended negative consequences** are being faced by those who suffer from Sickle Cell Disease.

Please allow me to use some personal information to give you an idea about the problem.

Some years ago, I had a very bad pain crisis and went to the emergency room at a Richmond hospital. I have written hospital treatment instructions signed by my doctor stating that I should receive up to 10 mgs of Morphine two to three hours apart for a Sickle Cell Pain Crisis. I had my Sickle Cell Data Sheet with the instructions on it in my wallet and presented it. I asked for 10 mgs of Morphine. Let us just say the ER doctor did not feel the need to follow the treatment plan listed and signed by my doctor. He would only give me 4 mgs. I suffered. I managed to call my doctor who called the hospital. Later on I was given more Morphine but still not what I needed.

Ten mgs of Morphine every two to three hours is the equivalent of 80 to 120 MME/day. Based on the CDC Dosing Guidelines, this would mean that after 10 to 15 hours I may not receive any more opioids or I would only receive 10 mgs every 5 hours or 8 mgs every 3 hours or some other version of use. Many patients require a higher dose of opioids. One patient I know required 15 mgs every 2 hours during his hospitalization. This is the equivalent of 180 MME/day. **If we need this much opioids in the future, will we receive it?**

During a hospital stay in January of 2017, my crisis was rough but I did not need 10 mgs of Morphine two to three hours apart. However, I did need a larger dose of opioids at the beginning then I received. After leaving the hospital, I calculated how much Morphine I was prescribed per day. The figure came to a total of 48 MME/day, 2 MME/day below the CDC guidelines. Was I given 48 MME/day as a deliberate action to stay below the CDC guidelines?

I visited my doctor in May of **2016** for my quarterly appointment and asked for a new prescription for 60 tablets of Demerol for home use. He wrote the prescription, but informed me that after July 1st he might only be able to write a prescription for 14 tablets every 3 months. He also said he was considering not writing prescriptions for opioids at all.

I visited my doctor in May of **2017** for my quarterly appointment and asked for a new prescription for 60 tablets of Demerol for home use because I was leaving within a few days on vacation. Further, the previous prescription was used in part, but the remaining pills would expire and no longer be effective by the end of the month. My primary care doctor of thirty years informed me that he would not write me a prescription and no longer writes anyone a prescription for opioids.

My doctor did refer me to a doctor that visited me in the hospital in January. She is a hematologist working with a cancer institute who also sees sickle cell patients. Her office required me to agree not to get opioids from any other doctor and I had to agree to be drug tested at any time, but did give me a prescription.

One of my other doctors has told me that he stopped writing prescriptions for opioids. My wife's doctor is limiting writing opioid prescriptions and the doctor for a friend's family member has stopped writing prescriptions for opioids. I am sure that these are only a few of many instances where doctors have stopped writing prescriptions for opioids. **Where are sickle cell patients going to go?**

The new CDC Guidelines on Long-Acting Opioids states the following:
"When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids." (recommendation category: A, evidence type: 4)

The PiSCES Study results in the Annals of Internal Medicine January 2008, suggests the pain pattern in persons with Sickle Cell Disease is normally daily. They are in chronic pain. On a pain scale of 1 to 10, their pain intensity is from 4 and 5 to 9 as a common occurrence. To deny all Sickle Cell Disease patients long-acting opioids would result in them being in the hospital more often for pain relief at a greater cost to the taxpayers because of a lack of insurance by many. At the very least they will be less functional and/or out of work more often.

Using opioids in Sickle Cell patients is generally safe. The CDC's own data shows that opioid deaths in Sickle Cell Disease are not increasing, and are rare. [Ruta NS, Ballas SK. The Opioid Drug Epidemic and Sickle Cell Disease: Guilt by Association. Pain Med. 2016 Oct;17(10):1793-1798.].

News Article
http://www.dallasweekly.com/health/article_786129b4-7918-11e7-899b-ef54de21cbf7.html

On July 19, 2017, the Dallas Weekly published an article entitled "War on Opioids Hurts Sickle Cell Disease Patients" and subtitled "Sickle Cell Disease Sufferers Trapped in Fight Against Opioid Scourge". The article states "so many of those suffering from sickle cell anemia are prescribed a variety of powerful pain killer derivatives." According to Judy Anderson, the Executive Director of Sickle Cell Association, Inc. based in Norfolk, VA, "a growing number of people who are suffering from sickle cell anemia may be severely impacted by the government's effort to curb opioid addiction."

Ms. Anderson was quoted as saying "One lady who called the office Monday, July 10th, told me she took her last pain pill the previous Friday," said Anderson. "Her doctor is reviewing her case and has not written her a new prescription." Anderson continued: "Unable to get her pain meds, I am sure she will end up in a hospital, because she went to the emergency room to have her pain treated."

"Anderson said that in April 2016, in the wake of the growing opioid addiction and related deaths due to overdoses, hospital emergency departments in Virginia received guidelines aimed at curbing opioid misuse and addictions."

"For the first time, the regulations apply specific guidelines to Virginia providers, dictating how many opioids can be prescribed depending on the situation and stipulating that other pain treatments should be considered before opioids are prescribed."

Other Information
It should be noted that only one hospital in our state (in Richmond) provides clinical care for adult patients. Based on over 40 years of working with the patient community, Judy Anderson of our Norfolk chapter has seen "those who use the emergency department as their adult source of

care and are at the mercy of just getting medications as a hit or miss attempt to relieve pain." She also states "the doctors here were sending patients to a Physical Therapist as their alternative to saying they were referring the patients for Pain Management."

CVS Announcement
It has been announced that CVS Pharmacies will only fill opioid prescriptions for 7 days. Will other pharmacies follow CVS's lead? If a doctor writes a prescription for opioids for 14 days, does this mean that a pharmacy will fill the order for 7 days and then fill the remainder the following week? Or will the patient have to get a new prescription? If a new prescription is needed, will the patient have to make a new doctor appointment? If so, this would be an additional cost to the patient and/or insurance company.

CIGNA Announcement
Starting in 2018, the health insurer Cigna Insurance Company, will no longer cover OxyContin, the branded version of the painkiller oxycodone. Cigna will still cover oxycodone alternatives to OxyContin. Will other insurance companies follow Cigna's lead? What effect will this have on the patient population?

What is going to happen to us? How much will I and others have to suffer?

It is my understanding that an exception or some allowance has been made in some guidelines for persons with cancer. **What I feel is needed is an amendment to the CDC guidelines or ANY other guidelines to state that "the dosing limits in the guidelines and restrictions on the use of long-acting opioids should NOT be applied to patients with Sickle Cell Disease" and have the amendment distributed to medical boards, hospitals and doctors.**

Please help us. Do not let us suffer from the backlash and unintended negative consequences of the opioid crisis.

Thank you for your consideration in this matter.

Due to an unavoidable conflict, I cannot attend the December 1 public meeting. Therefore, I am submitting comments for your consideration. I am a 79 year old male who suffers from osteoarthritis in one knee for which I take tramadol in addition to daily use of a compounded ointment, and monthly acupuncture treatments. The current treatment approach has proven an effective alternative to surgery.

I have studied data and statistics from the State and the Governor's Task Force on Opioids and do not understand how those statistics can justify the regulation that has been put into effect and is being considered for finalization.

According to a presentation by the Task Force, opioid prescription overdoses peaked in 2012 and dropped each year afterward. Between 2012 and 2016 the reduction was 18%. That clearly shows that education works. The data also confirm that the increase in opioid deaths is mainly due to illegal drug use, namely cocaine, heroin, and fentanyl. According to the Virginia Department of Health's fourth-quarter report for 2016, of the 1,420 drug-related deaths, 618 were fentanyl-related.

Robert DuPont (the first director of the National Institute of Drug Abuse) and William Bennett (the nation's first drug czar) have written, "70 percent of our nation's opioid deaths do not come via prescription abuse. ... The main problem today, and the growth for tomorrow, is illegal opioids such as heroin, illegal fentanyl, and a hundred other synthetics, not legal drugs used illegally or in ways not as prescribed." In 2015, there were 33,000 opioid overdose deaths with heroin deaths constituting almost 13,000 and synthetic opioids (mostly illegal fentanyl) another 9,600 deaths.

I recognize that for some the opioid problem starts with prescription narcotics that lead to addiction and then a search for cheaper opioids on the black market. However, that does not justify treating all prescribed opioids the same, given the documented progress made since 2012 and the potential of the prescription management system data base.

The risk of addiction from a class 4 opioid like tramadol is small but the impact of forcing patients to make quarterly doctor visits along with periodic urine tests is

not. Arthritis is mainly a disease of the elderly and the burden imposed on them is costly and unreasonable. According to the Kaiser Foundation, 50% of Medicare recipients had annual incomes of $24,150 in 2014. That means that the regulatory requirement for periodic doctor visits along with the urine tests is a regressive tax on those who can least afford it. I have been told that some patients have already decided to seek alternatives to tramadol and compliance. That is not encouraging from either a medical or potential abuse perspective.

I urge you not to treat all classes of opioids the same and to place greater reliance on the existing prescription management system to track potential over-prescribing. Most doctors want to do the right thing and will use the increased awareness to tailor prescriptions and monitoring to patient specifics. It should be self-evident that since all opioids do not carry the same risk of abuse and addiction that the stringency of requirements should be risk-related.

William O'Keefe
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Yeatts, Elaine J. (DHP)

From: David Falkenstein <falky1@cox.net>
Sent: Saturday, November 18, 2017 2:30 PM
To: Yeatts, Elaine J. (DHP)
Subject: Regulations Governing Prescribing of Opioids and Buprenorphine [18 VAC 85 - 21]

VIRGINIA ACADEMY OF PHYSICIAN ASSISTANTS

250 West Main Street, Suite 100
Charlottesville, VA 22902
434/977-3716 • Fax 434/979-2439
www.vapa.org • vapa@vapa.org

Elaine,
The Virginia Academy of Physician Assistants(AAPA) is supportive of the proposed regulatory changes Governing Prescribing of Opioids and Buprenorphine [18 VAC 85 - 21]. We appreciate the given ability for comment.

David Falkenstein PA-C
Chair Government Affairs Committee

Virginia.gov Agencies | Governor

Logged in as
Elaine J. Yeatts

Department of Health Professions

Board Board of Medicine

Chapter Regulations Governing Prescribing of Opioids and Buprenorphine [18 VAC 85 - 21]

Action	Initial regulations
Stage	Proposed
Comment Period	Ends 1/26/2018

All good comments for this forum Show Only Flagged

Back to List of Comments

Commenter: Melissa Messick 11/29/17 8:34 pm

Urinalysis Costs

I have a problem not with this law but with the cost to me and my insurance company, that I will explain in hopes of finding a solution. A brief Background:

I'm a 62 year old female I have documented cases of Arthritis, Sjogrens Syndrome, I also have had a pelvic sling which went very badly. These left me immobile due to swelling and pain, this was for the best part of two years. I was self-medicating with a lot Excedrin to be able to perform the smallest of daily living. My doctor that did the pelvic sling told me there was nothing else he could do for me. Two years ago my blood count bottomed out and I was hospitalized with only 4000 platelets which was life threatening.

Since that time several wonderful doctors have given me my life back. The medications and the doses were all trial and error to get to this point. I'm building myself back up and enjoying doing things with my children and grandchildren again. I am able to hold down my job now with the Virginia Employment Commission (pay band three.)

This new law that is in affect that states that I have to take a drug test every so often. I do not mind doing this. I took time off from my job and paid for an office visit that I didn't need. My doctor did the test and it was sent to Labcorp. The test came back as expected. Then I get a bill for the test at the cost of $221.00 for my part of the test and the insurance had to pay the remainder of the $425.00. I will still need to purchase the Medication. This something that I cannot afford and I certainly hate to go into debt for. I only take one Tramadol or two a day along with the other medications not on your list.

I hope you can see the issue I take with this Law. There are others I feel sure that are on a fixed income for example the elderly, terminally ill, cancer patients etc. that this will impact greatly. Again the elderly and the lower income population will not be able to received proper care.

I would be happy to speak to someone further.

Melissa Messick

lion6255@aol.com

Commenter: Debbie Peters 11/30/17 8:46 am

Urinalysis

I am in agreement with Ms. Keswick regarding the need for lab charges for urine testing each time a needed prescription has to be refilled. Who can afford this? I am State employee with insurance and wpykd struggle to make these payments monthly in addition to the cost of the medications. I cannot imagine how a lot of people without insurance or low paying jobs could manage. I think someone needs to reconsider this issue.

Commenter: Sharon Fassold 11/30/17 1:46 pm

Testing

While I agree with the spirit of the law, please reduce the cost of testing.

Commenter: Susan melton 11/30/17 7:08 pm

High cost of testing

I feel that this charge is astronomical to those of already struggling to pay for overpriced meds. It is unfair to legitimate people who need these meds.

Commenter: Brenda Crouch 12/3/17 6:16 pm

Testing Cost

For the average person this testing would be extremely high and time consuming.

Harp, William L. (DHP)

From: Harp, William L. (DHP)
Sent: Wednesday, December 27, 2017 2:52 PM
To: WH BALLARD
Cc: Yeatts, Elaine J. (DHP)
Subject: RE: Comment for proposed regulations regarding "Opioid Crisis"

Dear Mr. and Ms. Ballard:

Thank you for your comments.

I am not sure if you have read the proposed regulations, so I am attaching the text from Regulatory Town Hall. http://townhall.virginia.gov/L/ViewXML.cfm?textid=12132

The intent of the regulations, initially effective on March 15, 2017 and revised August 24, 2017, is to ensure that physicians/prescribers are more thoughtful in their assessment and treatment of acute and chronic pain, thereby enhancing patient safety. The Board is aware that some physicians are telling their patients that they must reduce the amount of opioid they are taking. The Board is also aware that a physician may tell a patient that he/she will no longer write opioids for chronic pain and that they must seek care from a pain management specialist. The Board was aware that some physicians took these stances after they received a memo about the Centers for Disease Control Guidelines in May 2016, which preceded the Board's development of regulations for Virginia licensees.

If you carefully read the regulations, they do not instruct a prescriber to reduce the amount of medication that has been effective and safe. The prescriber is authorized to use his/her discretion with the dosages written; there must be clear documentation of the rationale for higher doses that 120 Morphine Milligram Equivalents a day. Also, the prescriber is to ensure patient safety by writing a prescription for naloxone, the rescue drug for opioid overdose.

I am not sure of the coming restriction to which you refer. The regulations have been in effect for a little over 9 months.

The Bloomberg article has a statement from Dr. Ajay Manhapra, who was at 2 or more of the meetings the Board of Medicine had on these regulations. He has communicated with me since regarding a paper he co-authored on the difficulty of tapering long-term pain patients from their opioids. Again, the regulations give the prescriber discretion on how to adjust the medicines for a chronic pain patient.

I will make sure that your comments are reviewed by the Board of Medicine as it goes through the process of developing final regulations.

I hope this is helpful to you.

With kindest regards,

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

From: WH BALLARD [mailto:whballard1210@comcast.net]
Sent: Tuesday, December 26, 2017 9:00 PM

28

To: Harp, William L. (DHP) <William.Harp@DHP.VIRGINIA.GOV>
Subject: Comment for proposed regulations regarding "Opioid Crisis"

Dear Dr. Harp,

My wife and I hereby comment regarding Virginia's possible medical regulations regarding the "Opioid Crisis." We fully understand that there has been a rise in fatalities due to medically prescribed opiates for pain. However, making it impossible for doctors to, confidently and without fear, provide their patients in chronic pain with the necessary medicines is not a solution. We know that Virginia law currently allows doctors to prescribe opiates indefinitely to patients with chronic pain. However, there appears to be a disconnect between the spirit of the law and the actual administration. Unless you desire to have a rash of suicides resulting from an inability to obtain prescriptions in place of your overdoses, this must be recognized and addressed. Please see our experience as follows:

My wife has an autoimmune disease similar to Lupus. She began having pain in her joints in her late twenties which got progressively worse to the point where she could hardly walk. She has had two shoulder joints, a lower left leg bone replacement, and one hip replacement. She tried every known method of dealing with the pain which goes on day or night whether she is moving or still. She even tried acupuncture. She was sent to several different pain management specialists who tried various pain medications. One of her doctors was threatened by government agencies and could no longer treat his patients. Finally, our family doctor put her on enough prescription man made pain killers to allow her to function in a fairly normal manner. She has been on this treatment with minor increases for about 20 years. Now our doctor has informed us that the end of December the Virginia government is going to make it impossible for him to continue with her pain medication. He is gong to try to find her a pain management specialist but, we have been down that road before with no success. If she has to come off her medication, it may kill her. If it doesn't kill her she will be in such pain she may want to die. She is now 65 and her Lupus like disease has done great harm to her kidneys, her lungs and her heart and she has little strength with which to withstand more pain. We understand that this government program is an attempt to address the over use of legal drugs. My wife has never used her legal drugs in an illegal manner. There must be some way for you to help people in this position and allow their doctors to continue providing them them the drugs necessary to cope with their pain. Please, please put a stop to this coming restriction!

We have been in corresponding with Delegate Kirk Cox on this issue. The following is our latest letter to him. It includes a link to an article which we think expresses the problem extremely well. We would appreciate very much if you would read it.

Dear Delegate Cox,

We will be seeing our family doctor on Dec. 28th to ask if he will be willing to continue prescribing Sara's chronic pain medications. We will show him your previous letter which states that he can do so. However, If he still refuses, we will be at a loss. Please check out the included link below to see what our doctor and we will be facing. Thank you.

https://www.bloomberg.com/news/articles/2017-11-21/millions-of-patients-face-pain-and-withdrawal-as-opioid-prescriptions-plummet

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This concludes our comments regarding the proposed regulations! Thank you for your consideration of them.

Sincerely,

William and Sara Ballard.

1210 Covington Rd.

Colonial Heights, VA 23834-2716

Ph: (804) 520-4211

Harp, William L. (DHP)

From: mail@changemail.org
Sent: Wednesday, December 13, 2017 8:50 AM
To: Harp, William L. (DHP)
Subject: 100 more people signed "Terry McAuliffe: Virginia Opioid Treatment"

change.org New signatures

William L Harp – This petition addressed to you on Change.org has new activity. See progress and respond to the campaign's supporters.

Terry McAuliffe: Virginia Opioid Treatment
Petition by Steve M · 100 supporters

100 more people signed

View petition activity

RECENT SUPPORTERS

Kayla Vinson
Dante, VA · Dec 04, 2017

Why would anyone want to stop treatment with these medicines is beyond me and down right sickening to not help those who need it and are actually doing good with these medicines. Things aren't looking to getting better but worse in many ways,but let's keep supporting for what is right.

nancy Harvey
Coeburn, VA · Oct 05, 2017

These medications have helped so many. I

Savannah beckner
Hardy, VA · Sep 06, 2017

Because suboxone saved me life! I've been clean for 5 years now!

Kelly Hawley
Media, PA · Sep 06, 2017

Subutex saved my life. I don't feel the government should be able to regulate what our doctors feel can save our lives. Taking away these medications is only asking for addicts to go back to the streets and overdose on heroin. Due to the crackdown on everything else. This makes it seem as if the government's way of ending the epidemic, is to let addicts kill themselves off...not help save them!

Dorene Ernst
Burke, VA · Aug 22, 2017

Only doctors should decide this not politicians

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Petitioning Governor Terry McAuliffe and 1 other

Virginia Opioid Treatment Crisis

Steve M Princeton WV, WV

0

0 have signed. Let's get to 1,000.

Steve M
Princeton WV, WV

Virginia HB 2163 wants to restrict prescriptions and federally licensed OTP clinics from using mono buprenorphine (Subutex) for opioid dependence. The bill restricts it to only patients that are pregnant or patients that are switching from methadone to buprenorphine but they cannot have mono buprenorphine for more than 7 days, or whatever the Virginia board of medicine decides. This isn't a good idea, restrictions on prescriptions are fine but also allow people that cannot have Naloxone to also be able to get a prescription.

They need to also allow the federal OTP clinics to dispense it in take homes because the patients that have them earned them. I can see and understand why limits and things need to be put into place. It is not a good idea to make this bill law, though. The problem with the bill is the patients that are already in treatment, and have a documented hypersensitivity to Naloxone will lose access to treatment. Buprenorphine is the safest alternative of 3 medications available it doesn't matter if it has Naloxone

or not. Addiction is a fight these patients will have to fight with for life. The patients that have a hypersensitivity shouldn't lose access to this medication. It isn't right that if they didn't have a hypersensitivity they could continue getting Buprenorphine but with the Naloxone. Most doctors will not prescribe Subutex unless you cannot have Suboxone anyway.

Methadone, and Buprenorphine both are proven medications used to treat addiction. Each of these medications has their uses but some patients cannot have suboxone they need a full agonist such as methadone. Some patients cannot have methadone and seek suboxone treatment. Every patient deserves the right to what medication they are being treated with. Not one of them works for everyone. Patients that have gone to federally licensed clinic need to be allowed to still have take homes, take homes they earned. Buprenorphine has a ceiling effect anything above 32 milligrams cannot be processed in a 24 hour time period so the chances of overdose are way below the average of other medications used. Some of these patients have been in maintenance replacement therapy and cannot afford to go to the clinic every day to get it. I ask the state of Virginia to look at the facts and make a decision that would save many people's lives that suffer from addiction and opioid dependency.

All of these medications are effective in treating addiction. Restrictions on prescriptions are fine, but also allow patients that have a documented allergy on file to get a prescription so these patients don't lose treatment and also allow the federally licensed clinics to continue to dispense it in take homes. While methadone is stronger than buprenorphine some people need a stronger medication. Everyone is different, and as with many medical problems, you cannot put everyone on the same medication. Experts across the nation are concerned about this bill as it will put patients back on the streets.

Buprenorphine has been offered as an atlernative at federally licensed otps across the nation for over a decade in most places. These patients deserve the right to keep their treatment with Buprenorphine just the same as the Methadone patients. Not everyone can take Methadone, and everyone cannot take buprenorphine. Both of these medications are life savers and too take this option away from otp clinics put patients in danger. The reason they seek treatment at an OTP is because most doctors will write Buprenorphine anyway. It costs clinics more to carry the combination tablet and that costs the patients more hundreds of dollars a month more to be exact. Naloxone was put into Suboxone to appease the DEA.

Naloxone was also used to help the Reckitt-Benckiser the maker of Suboxone file a patent as regular Buprenorphine has been around for over 30 years so they couldn't patent it. Generic Buprenorphine came out 4 years before generic Suboxone did. That is because they couldn't hold a patent for plain buprenorphine as long. While both drugs have their uses, some people just cannot have Naloxone. These people shouldn't be punished for an allergy nor should the patients at otps lose treatment because of a bad company. Regular Buprenorphine was available as a generic to the public 5 years before generic Suboxone was and that is because Reckitt-Benckiser couldn't hold a patient to a drug they didn't invent.

The Virginia Medical board is going to make a seriously bad decision to stop these clinics from dispensing this medication if this bill is signed into law. Many of the biggest addiction organizations also believe this to be a bad law.
If they take Buprenorphine treatment away today, what will they do tomorrow? Go after Methadone? Both are these drugs have helped many people get their lives back. SAMHSA has deemed it a safer alternative and those are their words. not mine. If the plan is to also go after Methadone there will be an even bigger crisis on our hands. These systems work, and limiting options to patients isn't a wise or

just choice.

Virginia is full of rural areas and many people travel 50 plus miles one way to be able to get to dose. Until they earn their take homes they do this everyday, and it is extremely hard for these people to have a life, work, and everything in between. Most of these patients cannot travel every day to dose so I am asking you please do not punish the patients that have done what was are required by state and federal law to obtain take homes.

We need to have access to this medication, restrictions like that are not the answer. We are fighting a war and these medications need to be more accessible. I ask for the bill to be amended and allow people that have a hypersensitivity to Naloxone and have it documented to also be allowed to get a prescription and to allow federally licensed clinics to dispense it in take homes to the patients that have earned them. If they do not many of these patients will be forced to the streets more than likely, and if they overdose Narcan isn't an option because they are allergic to it. I believe every person should have a decision in what medication they are being treated with. All three of these medications have a potential for abuse, but methadone and suboxone aren't being limited. I believe if a patient has a documented hypersensitivity to Naloxone (Narcan) they should have the same access to therapy as a person would if they could have suboxone.

The OTPs are also conservative in providing patients with any take home medication. When take home medication is provided to the patient through the OTP, the OTP must meet eight clinical standards, which have been enforced singe the regulatory authority of the FDA that continued under the regulatory oversight of SAMHSA. These criteria include absence of recent drug abuse, which is determined through toxicology reports in addition to established regularity of clinic attendance, absence of serious behavioral problems, absence of known recent criminal activity, stability in the patient's home environment, length of time comprehensive maintenance treatment, ensuring that take home medication can be safely stored within the patient's home whether the rehabilitative benefit the patient derives from decreasing the frequency of clinic attendance outweighs potential risk. Compliance with the regulations is mandatory.

Restricting this medication will affect people currently in treatment at federally licensed facilities that already have diversion prevention protocols. Each take home at this moment is 1 days dose sealed in a bottle. So if a patient has 13 take homes he gets 13 sealed bottles. These bottles cannot be tampered with, if they were to be called in and a bottle be missing even the plastic on one before it was due to be taken the take homes are revoked.

Most patients being treated for addiction/opioid dependency get the combination pill anyway. Most patients that go to a clinic go because they cannot have suboxone or its the closest option they have.

These facts below represent all forms of buprenorphine products. Mono buprenorphine isn't the problem.

Patches
Tablets (Mono and Combined)
Buccal films
Sublingual Films

NATIONAL ESTIMATES FOR THE MOST FREQUENTLY IDENTIFIED CONTROLLED SUBSTANCES: Estimated number and percentage of total drug reports submitted

to laboratories from January 1, 2014, through December 31, 2014, and analyzed by March 31, 2015.

Buprenorphine drug reports represented only 1.01% of all drug reports Nationwide.

Inability to access to treatment is a predictor of increased use of diverted buprenorphine. The finding that the most robust risk factor for buprenorphine use was failing to access legitimate buprenorphine treatment implies that increasing, not limiting, buprenorphine treatment access may be an effective response to buprenorphine diversion among persons not in treatment.

Studies have shown that buprenorphine is safe and highly efficacious,(11)decreases hospital admissions, morbidity, and mortality;(12) reduces illicit opioid use; (13)increases treatment retention; (14)and is much more effective when used in ongoing maintenance treatment than when patients are tapered off the medication.(15)

(U.S. Drug Enforcement Administration, Office of Diversion Control. (2015). National Forensic Laboratory
Information System: Year 2014 Annual Report. Springfield, VA: U.S. Drug Enforcement Administration. Available at:
http://www.deadiversion.usdoj.gov/nflis/NFLIS2014AR.pdf

(Lofwall MR and Havens JR. Inability to access buprenorphine treatment as a risk factor for using diverted buprenorphine. Drug Alcohol Depend. 2012;126:379-383.+)

(11) Johan Kakko et al., 1-Year Retention & Social Function After Buprenorphine-Assisted Relapse Prevention Treatment
for Heroin Dependence in Sweden: a randomized, placebo-controlled trial, LANCET, VOL. 361 (Feb. 22, 2003).

(12)Sofie Mauger, Ronald Fraser, & Kathryn Grill, Utilizing buprenorphine to treat illicit and prescription opioid
dependence, NEUROPSYCHIATRIC DISEASE & TREATMENT 2014:10 587-598, 588 (2014).

(13) Roger D. Weiss et al., Adjunctive Counseling During Brief and Extended Buprenorphine Treatment for Prescription Opioid Dependence, ARCH. GEN. PSYCHIATRY (Dec. 2011), 9, available at
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3470422/

(14) Cindy Parks Thomas et al., Medication-Assisted Treatment with Buprenorphine: Assessing the Evidence," Psychiatric
Services in Advance, (Nov. 18, 2013), 7.

This petition will be delivered to:

- **Governor**
  Terry McAuliffe
- **Executive Director of Board of Medicine**
  William L Harp

Read the letter

Letter to
Governor Terry McAuliffe
Executive Director of Board of Medicine William L Harp

Virginia Buprenorphine Treatment doesn't need more restrictions it needs less restrictions. The amendment I purpose doesn't hurt anyone in the process. It puts the restriction in place, but also allows patients that cannot have suboxone to also be able to get a prescription. It also allows federally licensed clinics to dispense it in take homes because those patients went for a years to earn them. It isn't right, nor possible to make these patients travel 50 plus miles one way to dose than drive back. It puts undue hardships on patients in treatment already, and will have a drastic effect on these people's lives. If we could take a look at the data of diverted buprenorphine and that includes all forms of this medication with and without naloxone we would see the same results we did with Methadone. It was around 10 years ago that data was looked over and most of the diverted medication came from pain patients with little to no oversight. These clinics have multiple diversion protocols in place, and most patients suffering from opioid dependence cannot even get Buprenorphine Mono wrote to them anyway unless they cannot have Naloxone. Buprenorphine mono isn't the problem, the problem is treatment is inaccessible. Please take all of this information into consideration before making a decision that will alter thousands of Virginians life. I have linked multiple statistical facts, and the sources of those facts. Narcan isn't the deterrent in these drugs, it is buprenorphine itself. It binds to the receptors much more aggressively than other opioids and therefor makes those other drugs ineffective. Narcan has nothing to do with it, and all it effectively does is sky rocket the price of treatment because generics have to keep up with the price of brand names. I hope you make the right decision and support these people.

OK

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Today: Steve is counting on you

Steve M needs your help with **"Terry McAuliffe: Virginia Opioid Treatment"**. Join Steve and 501 supporters today.

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Today: Steve is counting on you

Steve M needs your help with "**Terry McAuliffe: Virginia Opioid Treatment**". Join Steve and 501 supporters today.

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English (United States)

- Certified B Corporation

English (United States)

Harp, William L. (DHP)

From: Harp, William L. (DHP)
Sent: Thursday, October 19, 2017 2:44 PM
To: Manhapra, Ajay; Brown, David (DHP)
Subject: RE: The conundrum of opioid taper

Thanks, Ajay.

I very much appreciate your attendance at the meetings of the Board and your evidence-based comments.

I believe that we may need to convene yet another Regulatory Advisory Panel in the months ahead, and the Board might ask you to serve on it.

WLH

From: Manhapra, Ajay [mailto:ajay.manhapra@yale.edu]
Sent: Thursday, October 19, 2017 8:00 AM
To: Brown, David (DHP) <David.Brown@dhp.virginia.gov>; Harp, William L. (DHP) <William.Harp@DHP.VIRGINIA.GOV>
Subject: The conundrum of opioid taper

Hello:
Hope yu both are doing well. I am attaching an article I cop-authored with Al Arias, an addiction psychiatry scholar from Yale and Jane Ballantyne, a preeminent national expert on pain from University of Washington. This provides some perspective regarding the difficulty of opioid taper in high dose patients. I hope this informs your thinking about the statewide problem.

I have another review coming out soon about the conceptualization and management of complex disabling pain among patients with dependence and addiction. I will forward youth when it comes out. We are in the process of converting that model into an intervention that can be implemented in resource limited environment. The next paper I am working on is one on how to explain complex neurobiology of chronic pain to patients and primary care providers in simple terms, so as to use appropriate treatments and limit inappropriate and harmful treatment.

Both these projects are partly inspired by the participation in the work group and the need I identified there. I thank you for inviting me.

So long

Regards
Ajay

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The conundrum of opioid tapering in long-term opioid therapy for chronic pain: A commentary

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ABSTRACT

Background: In response to the opioid epidemic and new guidelines, many patients on high-dose long-term opioid therapy (LTOT) for chronic pain are getting tapered off opioids. As a result, a unique clinical challenge is emerging: although many on LTOT have poor pain control, functional decline, psychiatric instability, aberrancies, and misuse, these issues may often worsen with opioid tapering. Currently, a clear explanation and practical guidance on how to manage this perplexing clinical scenario is lacking. *Methods:* The authors offer a commentary with their perspective on possible mechanisms involved in this clinical phenomenon and offer practical management guidance, supported by available evidence. *Results:* It is not well recognized that allostatic opponent process involved in development of opioid dependence can cause worsening pain, functional status, sleep, and psychiatric symptoms over time, and significant fluctuation of pain and other affective symptoms due to their bidirectional dynamic interaction with opioid dependence ("affective dynamism"). These elements of complex persistent dependence (CPD), the gray area between simple dependence and addiction, can lead to escalating and labile opioid need, often generating aberrant behaviors. Opioid tapering, a seemingly logical intervention in this situation, may lead to worsening of pain, function, and psychiatric symptoms due to development of protracted abstinence syndrome. The authors offer practicing clinicians management principles and practical guidance focused on management of CPD in addition to chronic pain in these difficult clinical scenarios. *Conclusion:* Awareness of the science of the neuroplasticity effects of repeated use of opioids is necessary to better manage these patients with complex challenges.

KEYWORDS
Chronic pain; long term opioid therapy; opioid dependence; opioid taper; management

Introduction

In response to the role of excess prescription opioid use in the opioid epidemic and emerging data regarding excess risks associated with long-term opioid therapy (LTOT) for pain, the new Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain proposed an upper safe limit of 90 milligram morphine equivalent daily (MMED), and a recommendation for opioid tapering and eventual cessation among those above safe limits if the risk benefit balance is not favorable.[1] An estimated 20% of patients on LTOT for noncancer pain in primary care report severe pain-related problems, high psychiatric illness load, and addictive behaviors, including aberrancies that significantly limited their life, often with high opioid doses,[2] i.e., perceived safety risk may appear to outweigh benefit.[3] Adhering to the recommendation of opioid taper among these patients, especially those with psychiatric comorbidity, will be particularly challenging. A recent report of a system-wide opioid tapering efforts in this population in primary care settings suggests limited success, with only 35% of the high-dose patients with high psychiatric comorbidity were successfully brought down below the safe limit of 120 MMED over a year and the success was mostly limited to lower dose levels of the high-dose group.[4]

The conundrum of opioid tapering

With increasing clinical experience of opioid tapering, a challenging therapeutic and clinical phenomenon is emerging: 2 clinical interventions exactly opposite in nature, continuation and discontinuation/taper of LTOT for pain, can often result in the same set of persistent symptoms. Although LTOT can lead to poorly controlled pain, poor psychosocial and functional status, psychiatric instability, aberrancies, and misuse among a proportion of patients, the logical therapeutic intervention of opioid tapering and discontinuation, on the other hand, can cause persistent worsening of these same issues (archetypal patient story in Box 1), leading to confusing clinical scenarios and sometimes disastrous consequences, including death.[5] Such challenging clinical scenarios will likely be more common in the coming years with mounting pressure to adhere to safe upper dose limits. Clinicians and patients facing this challenge need better understanding of the underlying phenomena and practical guidance to manage these patients.

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/wsub.

Box 1. Archetypal patient story

A 61-year-old patient with posttraumatic stress disorder (PTSD) and chronic pain due to degenerative spine disease was able to maintain a business and provide for his family with fentanyl patches (>400 MMED) to control his debilitating pain for over a decade. Over time, pain and function worsened; insomnia, anger, and depression slowly emerged, and PTSD worsened. He sought more opioids from physicians for better pain control and to maintain his functional life. He interpreted multiple failed attempts by himself to stop opioids as evidence that they were helping to manage the pain driven by advancing spine disease, which in turn was driving his psychiatric worsening. However, radiographic investigations revealed stable spine disease. He got no clear answers from physicians why his pain was increasing despite this and wondered if they missed something.

On one of the visits with his primary care provider (PCP), he was told about the new CDC guideline and the concerns about safety and inefficacy of high opioid doses and an opioid taper was offered. He was assured that the pain would be stable with dose reduction and he might actually do better. He reluctantly agreed, and the fentanyl dose was slowly tapered in half over next 3 months. However, his pain, function, mood, anger, insomnia, anxiety, and PTSD all worsened. His PCP advised him to stay the course, and he was offered additional support, including referral to substance abuse treatment. Neither the patient nor the substance abuse treatment program felt that he was addicted to opioids.

He eventually decided to change the PCP, and during the transition he obtained overlapping opioid prescriptions from 2 doctors. Interpreting this as opioid contract violation, his old PCP tapered him off opioids completely over a month, providing medications for opioid withdrawal symptoms that lasted over a week after the last opioid dose. Hearing about this, his new PCP also refused to prescribe him any opioids.

Over the next month, his pain and physical function continued to worsen, as did his emotional health. He became confined to a wheel chair, unable to work, severely limited by pain the whole day. He became despondent and suicidal. He could sleep only an hour and a half a night and was exhausted. He thought about getting heroin from the streets, but his moral upbringing and military training prevented him from doing so. He could not understand why the doctors would do this to him and leave him helpless. He wondered whether this was all due to pain that was not effectively treated.

Patient progress: Recognizing severe protracted withdrawals, he was initially restarted on long-acting morphine tablets 90 mg 3 times a day. His pain and psychiatric symptoms came under some control, but not back to his baseline. Gabapentin and duloxetine were tried, but he could not tolerate them. He was still confined to a wheelchair after 2 months. Morphine was discontinued, and he was started on buprenorphine/naloxone 8/2 mg sublingually 3 times a day. Within several weeks, his overall function markedly improved, including abandoning his wheel chair. He was more engaged in multimodal chronic pain treatment with increased physical activation and willing to explore psychotherapy for pain and opioid dependence. His psychiatric distress abated considerably, and he started having up to 6 hours of uninterrupted sleep on most nights. From the patient's perspective, he describes "getting my life back."

Neuroplastic mechanisms behind the clinical conundrum

The explanations for this phenomenon lie in a deeper understanding of how opioid tolerance and dependence interact with pain, analgesia, relief, and other related psychological symptoms through reward mechanisms and drive patients' opioid need. In this paper, we (1) first provide a commentary supported by available evidence on how the complex neuroplastic and behavioral effects associated with opioid dependence and tolerance could modulate pain and other clinical symptoms among patients on LTOT and undergoing taper, and (2) then describe management principles that offer practical guidance to clinicians based on the above and offer some recommendations regarding opioid taper and management.

Neuroplastic and behavioral modulation of pain with evolution of dependence

Pain and relief: Rewarding affective experiences

Although most patients and providers focus only on the intensity of the sensory perception of pain (nociception or the physical pain), the associated affective experiences, immediate unpleasantness and an extended pain affect (suffering), and the resulting overt behavioral response (moaning, altered activity, medication need and use, etc.) are essential to the overall experience of pain. The immediate unpleasantness involves very little cognitive processes, whereas the other extended affective experiences of pain (extended pain affect) are driven by complex cognitive processes involving memory, appraisals, and judgments that generates the meanings or the implications that pain holds for the patient's life and their future, which in turn fuels the pain-related suffering involving depression, frustration, anxiety, and anger (negative affective state) experienced by the patient.[6]

Once considered in this light, pain relief amounts to more than a reduction in physical sensation of pain (analgesia) that is often measured clinically using pain scales and mediated by nociceptive neural pathways, but it also involves a relief in the affective components of pain experience.[7] Newer neurobiological understanding posit that pain relief involves a significant measure of affective "rewarding" experience (see Box 2 for definition) mediated through mesolimbic reward and learning pathways involving endogenous opioid system, separate from pain pathways. The same relief-reward pathways are also shared by the processes that drive the experiences of relief from other distressing psychological symptoms, such as depression, anger, frustration, or anxiety (negative affective states), evoked by various psychiatric disorders, such as depression, insomnia, and posttraumatic stress disorder (PTSD), medical diseases, and external stress that play important roles in further shaping the overall clinical experience of pain.[7–15] Also, other addictive

Box 2. Definitions

Reinforcing	Behaviors associated with the stimulus tend to be repeated.
Reward	A stimulus interpreted by brain as positive or beneficial (positive reinforcing: e.g., hedonic effect), or avoiding negative outcome/injury or restoring normal affective tone (negative reinforcement: pain relief, avoiding withdrawals).
Tolerance	A decrease in the effect of the drug despite a constant dose, or a need for increased dose to maintain a stable effect.
Dependence	An adapted state due to excessive substance stimulation that can cause cognitive, emotional, or physical withdrawal symptoms when substance use is ceased. Physical withdrawal symptoms do not develop with every substance (e.g., cocaine), or in every one using a substance, and do not always indicate compulsive use/addiction. Physical dependence mechanisms are different from psychological dependence.
Addiction	Compulsive self-use despite negative consequences.

Note. DSM and ICD criteria for opioid use disorder/dependence are methods used to diagnose various levels of addiction. In practice, clinicians mostly use clinical gestalt based on their understanding of addiction.

substances such as cannabis that do not have a notable analgesia effect but has direct effects on relief and reward pathways can, on the other hand, potentially provide pain relief as evidenced recent popularity of "medical marijuana" for treatment of chronic pain (see Box 3, patient story 1).

Thus, even if purely physical nociception is one part of pain, the affective experiences are critical to the patient's experience of both pain and its relief. The affective balance between pain and relief involves reward systems, making them susceptible to neuroadaptive modulation of learning, memory, and behaviors. Repeated exposure to addictive substances such as opioids that provide pain relief and have direct effects on reward systems can lead to a particular type of such neuromodulation.

Opioids, pain relief, and reward: Boon and the curse

Analgesics such as nonsteroidal anti-inflammatory agents are thought to have specific effects mostly confined to the nociceptive pathways providing analgesia, whereas opioids have additional effects on reward pathways that mediate relief, thus directly alleviating immediate and extended negative affective states associated with pain.[7–16] Thus, opioids' mechanism of action putatively involves both direct analgesic effect (analgesic relief) and direct effect on relief (affective relief), making them much more appealing pain medications than nonopioids to many suffering from pain (see Figure 1).[17] On the other hand, repeated use of opioids coupled with a highly salient negative reinforcing reward (pain relief) can set off a chain of neuroplastic changes in reward-based learning and memory pathways and behavioral changes that lead to tolerance and dependence in many, and eventually addiction in a small proportion, similar to that seen with pleasure-seeking (hedonic) use, a positive reinforcing reward (see Box 2 for definitions[18]).[19–23]

Whereas the clinical picture of the progression from dependence to addiction is rather clearly discernible in hedonic use where opioid is a drug procured by the individual themselves, the picture is a bit murky in LTOT for pain where it is a medication offered or administered in relation to a clinician-identified pain care need, often if not exclusively based on a therapeutic relationship.[24] A more nuanced neurobehavioral understanding is required to interpret the clinical picture associated with increasing tolerance and dependence in patients with chronic pain and prescribed LTOT.

Opioid dependence and modulation of pain

Opioid tolerance (definition in Box 2), although well recognized, is often described just as an expected pharmacologic effect mediated by molecular mechanisms and receptor adaptations involving the dose, frequency, and duration of opioid administration that can be overcome by increasing opioid dose or opioid rotation, unless there is clear opioid addiction.[15,25–34] Similarly, the clinical effect of physiological dependence (definition in Box 2) is seen within the narrow confines of well-recognized acute opioid withdrawal symptoms that last for a short interval of about 4–10 days and are medically manageable.[35,36] However, there are several additional powerful effects of neuroplastic behavioral changes with repeated use of opioids associated with opioid dependence and tolerance that do not get enough attention from either physicians or patients. These include (1) opponent effect, (2) allostatic reset, (3) affective dynamism, and (4) protracted abstinence syndrome. These effects develop at varying levels in different individuals, and in a proportion of patients on LTOT for chronic pain (not in every one), the clinical sequalae of these effects can potentially cause dramatic changes of the clinical scenario in following ways:

1. Repeated use of opioids for pain can worsen pain and associated psychological symptoms experienced by the patient over time. However, each dose of opioids will still provide salient relief to the patient, albeit at a lower level.
2. Dependence (not necessarily addiction), when well established, interacts bidirectionally and dynamically with pain, other symptoms, stress, sleep, and psychological distress, causing significant lability of all these, driving up the perceived need for opioids and other medications, especially psychoactive ones, to control various symptoms.
3. Although an appealing option in many with above problems, a dose reduction or opioid cessation in those with well-established opioid dependence (not necessarily addiction), can often result in significantly worsened pain, psychiatric status, and medical condition that persist for months or weeks beyond acute withdrawals. This persistent state of "protracted abstinence syndrome" can often be relieved by reinstatement or substitution of opioids and might be resistant to other nonopioid and nonmedication treatments.

Box 3. Patient stories of complex persistent dependence and protracted abstinence syndrome

Patient story 1

A 45-year-old patient with PTSD developed chronic neck pain at the site of biopsy for a Hodgkin's lymphoma diagnosis that is under remission for over 5 years now. The patient was on LTOT for past 5 years with oxycodone 20 mg 4 times a day. However, the patient had significant volatility of pain and associated anger, depression, and anxiety requiring escalation of opioids for relief intermittently. Patient's PCP started a dose reduction, stating safety concerns based on CDC guidelines. The patient developed uncontrollable pain, anger, and anxiety with depressed mood and sense of worthlessness. The PTSD symptoms also worsened. He started using marijuana to control his symptoms. Patient expressed that although pain score was not reduced much, marijuana was giving relief from pain and other symptoms, allowing him to have some quality of life. However, marijuana use was not allowed by the clinic, resulting in administrative cessation of opioids. This led to angry confrontations with PCP and other providers, resulting in loss of health care provider.

The patient was diagnosed with complex persistent opioid dependence while on LTOT and protracted abstinence syndrome after dose reduction that escalated with cessation. Patient was restarted back on oxycodone at prior dose while engaged in stress management and psychoeducation regarding pain and dependence. He stabilized within a month regarding pain, other negative affective symptoms, and PTSD. The patient is trying to stop marijuana use and thinking over a switch to buprenorphine-based treatment of complex persistent dependence.

Patient story 2

A 55-year-old patient with discoid lupus and painful nonhealing ulcer of the lower extremity is maintained on high-dose LTOT for over 5 years. The patient's opioid dose steadily escalated to fentanyl patch 200 μg/hour every 72 hours and oxycodone 10 mg every 6 hours because of pain that worsened during the years of LTOT despite the wound staying stable. The pain relief from fentanyl patch reapplication was minimal and consistently wearing off after 1 day, and the oxycodone gave minimal relief for about an hour. Patient was spending the other 2 days in bed or in chair with legs up, unable to do even minimally physically challenging activities. Patient was despondent, as a big family event was coming up in 3 weeks and the patient would not be able to perform duties as the head of the family because of the physical limitations.

The patient was diagnosed with complex persistent opioid dependence and was initiated on buprenorphine/naloxone 8/2 mg sublingually twice a day. Pain stabilized and physical activity improved within 2 weeks. Patient was happily able to fulfill duties in the family event. Buprenorphine/naloxone dose was increased to 24/6 mg daily after 6 months when patient developed aseptic necrosis of the femoral head due to prolonged steroid use related to lupus. Patient remains stable a year after entering treatment and enjoys life to the fullest.

Patient story 3

A 53-year-old patient with multiple shoulder surgeries and chronic pain who was managed with high-dose opioid therapy (180 MMED) presented 1 year after his opioids being tapered off with a blood pressure (BP) of 245/128 mm Hg, severe chest pain, and diffuse body pain. Patient also reports severe depression, anxiety, insomnia, restless legs at night, and severe loss of functional status after opioid taper, and gives history of over 15 emergency room visits and few hospitalizations for high BP, stroke-like symptoms, and chest pain to rule out myocardial infarction. Patient's BP and other symptoms would come under control with nitroglycerine, multiple antihypertensives and intravenous opioids while in the hospital, and each time the patient would be discharged with multiple antihypertensives, but no pain medications. All work up was negative.

In the clinic, this was recognized as severe complex persistent opioid dependence with protracted abstinence syndrome and patient was induced on buprenorphine/naloxone and stabilized in a day on 8/2 mg twice a day. BP immediately came down, and pains resolved within an hour. By 48 hours, the patient was back to normal clinically and fully functional as 2 years back. However, patient missed appointments and forgot to refill buprenorphine after a month and was readmitted to the hospital for a day with chest pain and high blood pressure again. Patient was reinitiated on buprenorphine/naloxone at prior dose with stabilization. A close case management plan was also instituted to help the patient with buprenorphine adherence.

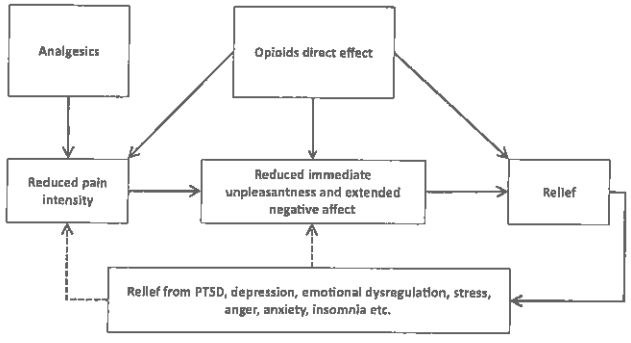


Figure 1. Multimodal action of opioids in pain relief.

Although not well recognized in relation to therapeutic opioid use in pain, these ideas are fundamental to our current understanding of the development of dependence and addiction. It is not necessary for a patient to have a full-blown addictive disorder in order to develop the protracted abstinence syndrome from opioids; LTOT as a part of legitimate treatment is sufficient cause. A brief mechanistic insight into these elements is provided in the following sections.

Opioid dependence and allostatic opponent effect

Richard Solomon introduced the concept of opponent process in 1970s to explain motivational behavioral changes in

development of addiction. Evocation of behavioral processes that changes the affective balance (unpleasant to unpleasant or negative to positive valence), as in opioid use for pain relief, results in a secondary "opponent effect" shortly after the primary effect, i.e., pain after initial relief or distress after initial pleasure. The opponent effect that is insignificant in the beginning grows in magnitude with repeated behaviors, resulting in declining magnitude and shorter duration of the primary effect.[7,15,33,37] In the case of repeated use of opioids for pain, the growing opponent effect of pain after initial relief results in reduction in quantity and duration of the net relief after each opioid administration (Figure 2).[8,37–39] This is a behavioral and experiential effect separate from or in addition to the withdrawal hyperalgesia and opioid-induced hyperalgesia, a noxious sensory phenomenon.[7,15,37,39,40] A similar behavioral effect can be expected with other negative affective states such as depression, anger, and anxiety that are often relieved by opioid administration, whereby these symptoms worsen and the relief after each opioid administration diminishes with repeated opioid exposure.[39] All these together may tend to increase the patient's perceived opioid need (Box 3, patient story1).

Cessation of opioids, the apparent logical intervention that can relieve the opponent effect,[15,37] often becomes impossible in a proportion of patients due to another concomitant change, "allostatic reset," a physiological process fundamental to the understanding of the progression of dependence that contributes to the increasing opioid need experienced by the patient.[21,23,37] Allostasis can be defined as the response of organisms to persistent external and internal demands, by which stability is maintained through change, achieving a state of chronic deviation of the regulatory system outside of the normal parameters (allostatic state) with establishment of a new set point (allostatic reset). The brain introduces experiences, memories, anticipation, and reevaluation of anticipation of needs to meet the physiological requirements of this new allostatic state.[23] With regards to pain and repeated opioid use, the baseline level of pain, suffering, and opioid need to maintain a new balance gets reset to higher points (see Figure 2). The allostatic reset together with the opponent process establishes a state of persistent pain and suffering interspersed with short-lived relief after each opioid administration (Box 3, patient story 2).[8,37–39] Reversibility to lower levels often becomes difficult, as the accompanying behavioral modifications that sustain this allostatic state gets hardwired. Opioid cessation or dose decrease can often lead to induction of behavioral changes (opioid seeking) driven by the automatic physiological need to reestablish prior allostatic state and avoid withdrawals.[23]

Taken together, allostatic opponent process provide a plausible explanation of worsening pain, function, and psychiatric instability and increasing opioid need associated with LTOT for pain, as in the clinical cases presented (Boxes 1, 3, and 4).

Affective dynamism

Tolerance and dependence are not static phenomena with stable levels of severity, but, rather, dynamic processes that interact bidirectionally with the associated symptoms and internal and external environments of the individual. Stress, anxiety, depression, anger, insomnia, irritability, and expressions of psychiatric disorders such as PTSD can alter moment to moment the level of tolerance and dependence and opioid need experienced by the patient, and vice versa, both during opioid maintenance and protracted withdrawal state. This sets up a state of lability/fluctuation of psychiatric symptoms and associated affective states such as anger, frustration, distress, depression, and anxiety ("affective dynamism") and emotional dysregulation in people on LTOT, which in part explains erratic behavior, including

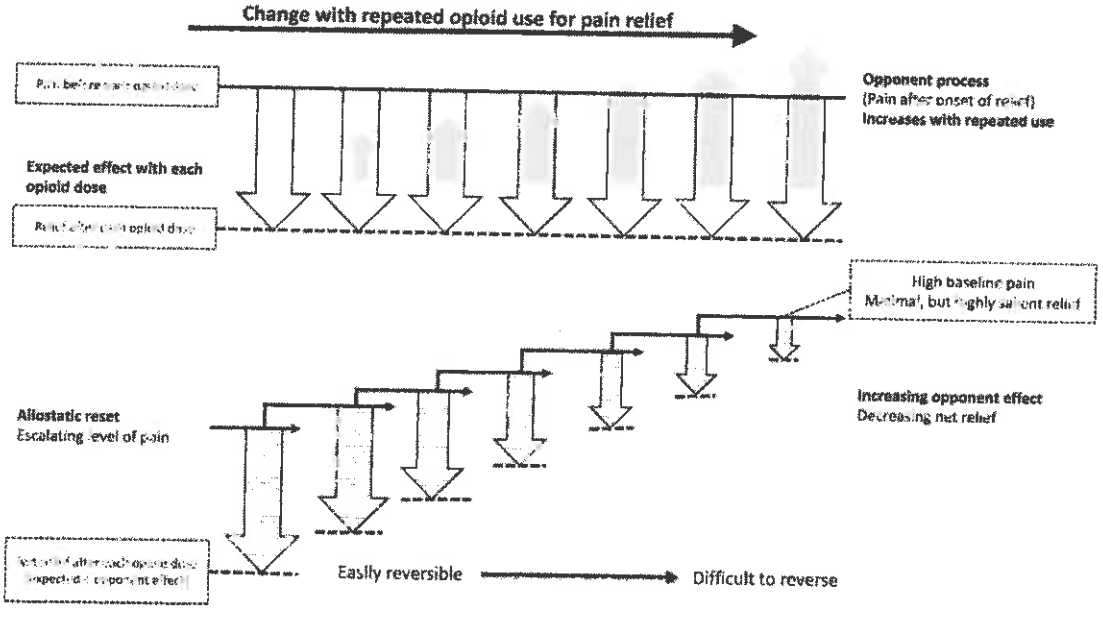


Figure 2. Graphical representation of the mechanism of worsening pain and decreasing relief with long-term use of opioids for pain: Allostatic opponent process in complex persistent dependence.

Box 4. Patient stories of challenges with management of complex persistent dependence

Patient story 4

A patient in the 40s with borderline personality disorder (BPD), PTSD, and frequent exacerbations of chronic back pain continued to have chronic abdominal pain with frequent exacerbations associated with severe anxiety, panic, PTSD symptom exacerbations, and uncontrollable nausea, vomiting, and diarrhea, many years after curative ileal resection for Crohn's disease. Despite high-dose LTOT (>500 MMED) using a combination of fentanyl patch, hydromorphone, and oxycodone, patient required 2 or 3 emergency room (ER) visits during most weeks. The patient was usually treated with intravenous hydromorphone, fluids, and bowel rest and discharged home in a day or two.

A diagnosis of complex persistent dependence was made as a unifying explanation for the exacerbation of pain, anxiety, PTSD, and gastrointestinal (GI) symptoms. Patient was started on buprenorphine/naloxone 8/2 mg 3 times daily, and all the symptoms settled down quickly. Slowly the patient engaged in treatment for PTSD and BPD. Patient says, "I am a new person. I still get pains, but it is not so bad as it was, and I don't feel the necessity to visit ER." Patient had to visit ER only once in the past year after being started on buprenorphine.

Patient story 5

A 62-year-old patient with multifocal chronic pain syndrome and brittle diabetes with peripheral neuropathy following complications of liver transplant over a decade back for liver failure from for transfusion acquired hepatitis C was on oxycodone 10 mg 4 times a day and gabapentin for over a decade. The pain started getting worse a year back, and patient used some extra oxycodone and started drinking alcohol to treat pain. PCP tapered patient off opioids because of aberrancy. The diabetes got worse and immunosuppressive therapy became inconsistent, and patient also lost PCP in the process. As pain and mood got dramatically worse within a few months, patient started snorting heroin for pain relief, which progressed within a few months to intravenous heroin, using his insulin needles. Patient overdosed 6 times in a few weeks, and the police directed patient to care.

Patient was diagnosed as complex persistent dependence and protracted abstinence syndrome after opioid cessation, which then progressed to opioid use disorder (intravenous heroin). Patient was reluctant to pursue OUD care, as local clinic was able to provide buprenorphine only if patient was willing to participate in onerous intensive outpatient program (IOP) requiring daily visits and they were explicit that pain will not be and cannot be addressed by buprenorphine (a common misconception in addiction world). Because of this experience, the patient was resistant to buprenorphine and methadone, and methadone was too risky considering his medical state. The pain clinic did not have buprenorphine availability at that time.

Based on a harm reduction approach, patient was started back on oxycodone under close supervision (weekly physician visits for prescription, urine toxicology, and counseling, and close family supervision) with intention of keeping the patient engaged in treatment and see if heroin use would stop once pain is controlled (as patient claimed it would). Pain was dramatically better, but oxycodone was wearing off too soon. Patient stopped using heroin and drinking alcohol for a few weeks. However, patient started using heroin again for pain control, but at much lower frequency and dose. After a few weeks, the patient came to self-realization that there was a heroin problem that needed to be addressed urgently and voluntarily entered buprenorphine IOP program, this time with assurance from current provider that buprenorphine treatment will also address pain. After a bit of struggle on lower doses, patient stabilized on 16 mg daily dose of buprenorphine. Patient now has manageable pains, and diabetes and transplant care is back on track.

Patient story 6

A 43-year-old patient with chronic foot pain from work-related stress fractures was requiring 50 mg of methadone daily for pain control. Patient's PCP reduced methadone to 30 mg daily in 8 weeks, and pain, mood, and functionality worsened and patient experienced withdrawals, frequently compromising ability to work and take care of family. Patient reported no psychiatric disease other than difficulty in managing family stress. A diagnosis of complex persistent dependence was made, and patient was reinitiated on prior dose. Patient regained excellent pain control and functionality. After extensive psychoeducation, patient decided to pursue slow opioid taper under her control with physician support. Methadone was slowly tapered off completely in a year, and pains persisted, but not distressful as before. Over next 2 months, patient started experiencing symptoms similar to physical withdrawals with exertional fatigue or towards night, and these were severely distressful. This was diagnosed as protracted abstinence syndrome, and patient was started on buprenorphine/naloxone 2/0.5 mg daily with a goal of slow taper over next 6–12 months (first to extend the dosage duration, i.e., 2 mg every other day after 2 months, then every 3 days and 4 days and then reducing the dose before stopping). Patient's symptoms and discomfort resolved, and the patient is committed to opioid taper.

threatened and actual violent behavior and suicides among patients.[20,41,42] This "affective dynamism" often imposes escalation and lability of opioid need while the patient is on steady opioid dose or during taper (Box 3, patient stories 1, 2, and 3; Box 4 patient story 4).

Protracted abstinence syndrome

With regards to withdrawals from opioid or any substance, there is scientific evidence of presence of both acute and protracted phases of withdrawal, but acute withdrawal gets the

most attention of patients and providers, probably because of its dramatic physical presentation over a short interval of about 4–10 days.[35,36] Varying degrees of protracted withdrawal emerge following acute withdrawal, a condition referred to as "protracted abstinence syndrome" that can last for months or years in people with long-standing opioid dependence.[36,43] This is presumed to be due to the hard-to-reverse allostatic changes associated with progression of tolerance and dependence.[23] Extended withdrawal symptoms specific to protracted abstinence in opioid dependence include anxiety, depression, sleep disturbances, fatigue, dysphoria (i.e., feeling down or emotionally blunted), irritability, decreased ability to focus, and deficits in executive control that can last for months beyond the period of acute withdrawal. The larger phenomenon of protracted opioid abstinence syndrome involves varying levels of rebound and reemergence of original symptoms (pain and disability in this case) and comorbid psychiatric disorders (such as PTSD) and medical comorbidities, in addition to opioid-specific protracted abstinence symptoms (e.g., Box 4, patient story 4).[43] The original symptoms and comorbid disorders may be experienced at higher levels of distress than before opioid initiation due to allostatic changes. Severe protracted abstinence syndrome after opioid cessation among LTOT patients can possibly lead to illicit prescription opioid or heroin use with rapid development of opioid use disorder (Box 4, patient story 5). Protracted abstinence syndrome offers a plausible explanation for persistent suffering with opioid dose reduction and cessation as seen with the archetypal patient and other patient stories described (Boxes 3 and 4).

When tapering opioids among those on LTOT, especially those with comorbid psychiatric disease, the clinician has to be aware that protracted abstinence syndrome phenomena can potentially expose patients to substantial risk of physical, functional, medical, and psychiatric instabilities along with harmful behaviors such as suicide and violence and relapse of substance use disorder (SUD), including opioid use disorder (OUD) (Boxes 1, 3, and 4).[5,43,44]

Management principles

Complex persistent dependence, the gray area between dependence and addiction

A clear diagnostic dichotomy of OUD versus no OUD dictating discrete management pathways would be optimal, especially for primary care physicians trying to triage care in patients with complex pain on LTOT. However, as elegantly pointed out by Ballantyne et al., a diagnostic distinction between dependence and addiction is nearly impossible in many patients on LTOT with the available criteria,[20] creating a diagnostic and therapeutic orphan status for these patients, somewhere in the gray area between the clear demarcations of simple dependence and frank addiction.[24] Ballantyne et al.[20,24] put forth the term "complex persistent dependence" (CPD) to describe the physiological and clinical state that exists in this gray area.

Clinically significant CPD can be recognized as a patient's desire to continue or increase the dose of LTOT, or inability to discontinue LTOT despite a prescriber's recommendation to discontinue it. The symptoms of CPD include worsening pain, function, affective symptoms and sleep disturbance, affective dynamism with escalating opioid need while maintained on LTOT, and protracted withdrawal syndrome on opioid dose reduction or cessation.

Based on typological classification and description of primary care patients with chronic pain on LTOT,[2] it is reasonable to hypothesize that having ≥100 MMED opioid dose and/or significant pain dysfunction, aberrancies and misuse, psychiatric burden, and prior history of or active SUD offers an easy cutoff for primary care providers (PCPs) to identify these difficult-to-manage patients with high likelihood of CPD that may cause significant persistent adverse effects with opioid dose tapering. Real-life experiences suggested that attempt at opioid taper is difficult in patients with chronic pain and high opioid doses.[4] These patients may have little insight into the role opioids are playing in their current state and thus may have little motivation and significant fear related to making a change.

Treatment approach in complex persistent dependence

Among those who develop significant CPD on LTOT, escalation of opioid doses for better pain control can often paradoxically result in worsening pain and poor functionality. At this stage, pain, insomnia, and affective instabilities are largely the symptomatic expressions of CPD (Box 4, patient story 4). A therapeutic focus on these peripheral symptoms without adequate management of dependence is unlikely to yield clinical success and often leads to potentially dangerous psychoactive polypharmacy, including antidepressants, antipsychotics, benzodiazepines, muscle relaxants, z-drugs, and stimulants.

Buprenorphine, a useful tool in complex persistent dependence

Buprenorphine, a partial mu-opioid agonist with a ceiling effect on side effects such as sedation, constipation, and hedonic properties, but no clinically relevant ceiling effect on analgesia, is emerging as a helpful analgesic agent in patients with poorly controlled chronic pain with full agonist opioids such as morphine, oxycodone, fentanyl, and hydromorphone. It offers good analgesia and effective treatment of dependence through its long half-life.[45–48] These properties can allow the patient to stop the full agonist opioid therapy that is potentially worsening the pain and function through CPD, and switch to buprenorphine, which is associated with lower levels of dependency and comparatively higher levels of safety. Once transitioned to buprenorphine, it can either be continued or tapered in a slow fashion that is often more comfortable to the patient.

We have found buprenorphine dosed multiple times a day (also known as split dosing, e.g., 8 mg 2–4 times a day) to be effective for many patients with chronic pain and CPD. Patients have to discontinue other opioids at least 8–12 hours before initiating buprenorphine to avoid induced withdrawals. Stopping the opioids in evening and initiating buprenorphine next morning is an easy strategy. A switch from methadone is often better tolerated when it is 40 mg or below daily dose. Home-based induction is convenient, patient friendly, and less resource intense when compared with office-based induction and is safe when deployed with proper education and support.

Close patient-centered engagement with their providers is an integral part of their effective treatment. Both patients and providers need education regarding chronic pain and opioid dependence/tolerance. Psychotherapies focused on chronic pain and opioid dependence can be effective. Other multimodal therapies for chronic pain may be more acceptable to treatment-resistant patients with chronic pain after the affective dynamism or protracted abstinence are ameliorated with adequate treatment of CPD with buprenorphine. Details of the progress of archetypal patient and other patients with treatment of CPD is provided in Boxes 1, 3, and 4.

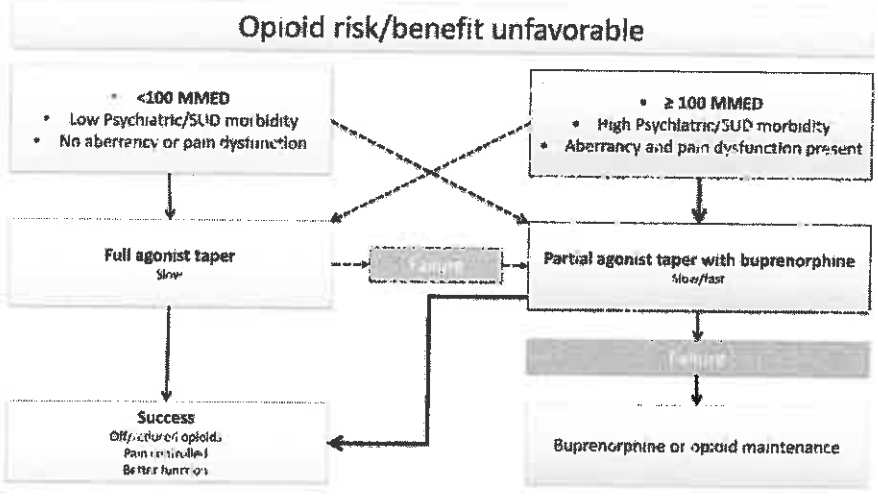
Methadone also can be helpful,[49,50] especially when buprenorphine is not tolerated by patient or available. But, full agonist properties raise the problem of worsening CPD with time, which is less of a problem with buprenorphine. Unlike the general assumption, a special "X" license is not required for use of sublingual formulations of buprenorphine for pain, and the Drug Enforcement Agency (DEA) does not prohibit the use of sublingual buprenorphine formulations for treatment of pain.[51] In fact, the Substance Abuse and Mental Health Services Administration (SAMHSA) guidelines on buprenorphine in opioid addiction (TIP 40, page 76) endorses that OUD patients with uncontrolled pain can be treated with split doses of buprenorphine in settings outside of substance abuse treatment program such as primary care clinics or specialty clinics if indicated.[52] However, misinformed local insurance and pharmacy formulary restrictions may often disallow such use of buprenorphine for pain. In that case, we recommend making a clinical diagnosis of opioid dependence collaboratively with the patient and then starting the buprenorphine substitution when indicated. More recently, transdermal and buccal formulations of buprenorphine have been approved by the Food and Drug Administration (FDA) for pain management, and clinical experience is growing with these medications.

A proportion of patients with CPD may not tolerate buprenorphine or methadone and will not be a safe candidate for methadone treatment. In these patients, providers and patients are often left with the hard choice of continuing full agonist opioids, acknowledging the risks involved or choosing the difficult task of slow opioid tapering. If opioids are continued, we recommend managing pain exclusively with scheduled opioid doses, preferably long-acting ones, avoiding as needed doses for breakthrough pain.

A patient-centered opioid taper plan

Many with simple dependence or CPD, especially those on low daily dose and low psychiatric comorbidity, may tolerate opioid taper (Box 4, patient story 5). When starting an opioid taper plan, it is particularly important to define what "success" in an opioid taper means. It should be much more than a simple reduction in dose. An opioid taper can be considered successful only if the probable risk improvement with dose reduction can be balanced with the degree of achievement of goals that are important to patient, namely, stability or improvement in pain and function, avoiding instability and harm related to medical, psychiatric, and psychological conditions and avoiding significant protracted abstinence syndrome. The process should also assure that patents feels that they are treated with dignity and respect, are involved in decision process, and remain engaged in continued treatment.[53] Patient involvement in decision and taper plan with support and psychoeducation is critical to its success (Box 4, patient story 6). Forced involuntary tapers can result in poor outcomes and patients feeling abandoned (Boxes 1, 3, and 4).[5]

If an opioid taper is considered in patients maintained on LTOT for many years, based on our clinical experience, we propose an opioid taper plan as illustrated in Figure 3 that offers 2 pathways based on the patient's current daily opioid dose. As stated above, ≥100 MMED opioid dose and/or significant pain dysfunction, aberrancies and misuse, psychiatric burden, and prior history of or active SUD offers an easy cutoff to identify high likelihood of CPD that may cause significant persistent adverse effects with opioid dose tapering. Among those with opioid dose of ≥100 MMED and/or significant psychiatric comorbidity, pain dysfunction, and opioid aberrancy, a rotation to the partial agonist buprenorphine, followed by a taper, is the preferred way, whereas a full agonist opioid taper can be tried among those on <100 MMED and/or with low psychiatric comorbidity, pain dysfunction, and aberrant behavior. If the full mu-agonist taper fails, the patient can be rotated to



MMED: Milligram morphine equivalent daily; SUD: Substance use disorders

Figure 3. A patient-centered opioid tapering plan.

buprenorphine and tapered (Box 4, patient story 6). If both taper attempts fail, we recommend pain treatment maintenance with buprenorphine (e.g., archetypal case). Although often stated as easy and straightforward, opioid tapers can often become challenging. Attempts at opioid taper have to be realistically tempered by the evidence that small studies have reported high failure rates with both full agonist and buprenorphine-based opioid tapers.[54,55] Clinical trials are needed to further develop and test these approaches.

In some patients on LTOT, an opioid taper is much more a complicated medical intervention than, for example, discontinuing a blood pressure medication because of the possibility of significant protracted withdrawal symptoms developing in a proportion of patients. Therefore, we recommend primary care physicians embarking on tapering plan to be cognizant of this serious adverse effect of opioid tapering and prepare contingency plans if required. These real issues need to be discussed with patient before starting opioid taper.

Conclusions

Many of the patients with chronic pain on LTOT exist between the gray area between simple dependence and addiction. The patients in this gray area probably have complex persistent dependence with allostatic opponent effect causing worsening pain and function, sleep disturbance and psychiatric symptoms, and affective dynamism causing fluctuation of these symptoms that drive opioid need of the patient leading to aberrant behaviors. Opioid dose reduction or cessation may lead to worsening of these symptoms and pain and function due to development of protracted abstinence syndrome. This makes continuation and withdrawal of LTOT infinitely complex and difficult therapeutic maneuvers for the patients and providers. A management plan focused on the syndrome of complex persistent dependence in addition to chronic pain would be more successful in these patients. Awareness of the science of neuroplastic changes associated with opioid dependence and addiction and its interaction with psychiatric illness is necessary for the good management of these patients. Theory-based clinical research focused on opioid dependence/tolerance rather than pain alone is lacking in this field and much needed.

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Author contributions

AM developed the original concept, produced the first draft of the manuscript and revisions. JB and AA refined the concept, reviewed the first draft and the revisions of the manuscript and provided significant editorial feedback.

References

1. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain–United States, 2016. *MMWR Recomm Rep.* 2016;65:1–49. doi: 10.15585/mmwr.rr6501e1. PMID: 26987082
2. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain—development of a typology of chronic pain patients. *Drug Alcohol Depend.* 2009;104:34–42. doi: 10.1016/j.drugalcdep.2009.03.021. PMID: 19473786
3. Von Korff MR, Franklin G. Responding to America's iatrogenic epidemic of prescription opioid addiction and overdose. *Med Care.* 2016;54:426–429. doi: 10.1097/MLR.0000000000000537. PMID: 27075900
4. Weimer MB, Hartung DM, Ahmed S, Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Subst Abus.* 2016;37:141–147. doi: 10.1080/08897077.2015.1129526. PMID: 26685018
5. Weeks WB. Hailey. *JAMA.* 2016;316:1975–1976. doi: 10.1001/jama.2016.10251. PMID: 27838720
6. Riley JL, Wade JB. Psychological and demographic factors that modulate the different stages and dimensions of pain. In: Price DD, Bushnell MC, eds. *Psychological Methods of Pain Control: Basic Science and Clinical Perspectives.* Seattle, WA: IASP Press; 2004:19–42.
7. Leknes S, Brooks JC, Wiech K, Tracey I. Pain relief as an opponent process: a psychophysical investigation. *Eur J Neurosci.* 2008;28:794–801. doi: 10.1111/j.1460-9568.2008.06380.x. PMID: 18671736
8. Seymour B, O'Doherty JP, Koltzenburg M, et al. Opponent appetitive-aversive neural processes underlie predictive learning of pain relief. *Nat Neurosci.* 2005;8:1234–1240. doi: 10.1038/nn1527. PMID: 16116445
9. Leknes S, Berna C, Lee MC, Snyder GD, Biele G, Tracey I. The importance of context: when relative relief renders pain pleasant. *Pain.* 2013;154:402–410. doi: 10.1016/j.pain.2012.11.018. PMID: 23352758
10. Franklin JC, Puzia ME, Lee KM, et al. The nature of pain offset relief in nonsuicidal self-injury: a laboratory study. *Clin Psychol Sci.* 2013;1:110–119. doi: 10.1177/2167702612474440.
11. Navratilova E, Morimura K, Xie JY, Atcherley CW, Ossipov MH, Porreca F. Positive emotions and brain reward circuits in chronic pain. *J Comp Neurol.* 2016; 524(8):1646-52. doi: 10.1002/cne.23968. PMID: 26788716
12. Zubieta JK. Pain signal as threat and reward. *Neuron.* 2010;66:6–7. doi: 10.1016/j.neuron.2010.04.002. PMID: 20399723
13. Fields HL. Understanding how opioids contribute to reward and analgesia. *Reg Anesth Pain Med.* 2007;32:242–246. doi: 10.1097/00115550-200705000-00012. PMID: 17543821
14. Navratilova E, Porreca F. Reward and motivation in pain and pain relief. *Nat Neurosci.* 2014;17:1304–1312. doi: 10.1038/nn.3811. PMID: 25254980
15. Baker TB, Tiffany ST. Morphine-tolerance as habituation. *Psychol Rev.* 1985;92:78–108. doi: 10.1037/0033-295X.92.1.78. PMID: 3983304
16. Howe CQ, Sullivan MD. The missing 'P' in pain management: how the current opioid epidemic highlights the need for psychiatric services in chronic pain care. *Gen Hosp Psychiatry.* 2014;36:99–104. doi: 10.1016/j.genhosppsych.2013.10.003. PMID: 24211157
17. Lee MC, Wanigasekera V, Tracey I. Imaging opioid analgesia in the human brain and its potential relevance for understanding opioid use in chronic pain. *Neuropharmacology.* 2014;84:123–130. doi: 10.1016/j.neuropharm.2013.06.035. PMID: 23891639
18. Hyman SE, Malenka RC. Addiction and the brain: the neurobiology of compulsion and its persistence. *Nat Rev Neurosci.* 2001;2:695–703. doi: 10.1038/35094560. PMID: 11584307
19. Meyer PJ, King CP, Ferrario CR. (2015) Motivational Processes Underlying Substance Abuse Disorder. In: Simpson E., Balsam P. (eds) *Behavioral Neuroscience of Motivation.* Current Topics in Behavioral Neurosciences, 27: 473–506. Springer, Cham.
20. Ballantyne JC, Sullivan MD, Kolodny A. Opioid dependence vs addiction: a distinction without a difference? *Arch Intern Med.* 2012;172:1342–1343. doi: 10.1001/archinternmed.2012.3212. PMID: 22892799

21. Koob GF, Le Moal M. Review. Neurobiological mechanisms for opponent motivational processes in addiction. *Philos Trans R Soc Lond B Biol Sci*. 2008;363:3113–3123. doi: 10.1098/rstb.2008.0094. PMID: 18653439
22. Koob GF, Stinus L, Le Moal M, Bloom FE. Opponent process theory of motivation: neurobiological evidence from studies of opiate dependence. *Neurosci Biobehav Rev*. 1989;13:135–140. doi: 10.1016/S0149-7634(89)80022-3. PMID: 2682399
23. Le Moal M, Koob GF. Drug addiction: pathways to the disease and pathophysiological perspectives. *Eur Neuropsychopharmacol*. 2007;17:377–393. doi: 10.1016/j.euroneuro.2006.10.006. PMID: 17169534
24. Ballantyne JC. Assessing the prevalence of opioid misuse, abuse, and addiction in chronic pain. *Pain*. 2015;156:567–568. doi: 10.1097/j.pain.0000000000000105. PMID: 25630030
25. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. *MMWR Recomm Rep*. 2016;65:1–49. doi: 10.15585/mmwr.rr6501e1. PMID: 26987082
26. Lembke A. Why doctors prescribe opioids to known opioid abusers. *N Engl J Med*. 2012;367:1580–1581. doi: 10.1056/NEJMp1208498. PMID: 23094719
27. Eisenberg E, Suzan E, Pud D. Opioid-induced hyperalgesia (OIH): a real clinical problem or just an experimental phenomenon? *J Pain Symptom Manage*. 2015;49:632–636. doi: 10.1016/j.jpainsymman.2014.07.005. PMID: 25128284
28. Yi P, Pryzbylkowski P. Opioid induced hyperalgesia. *Pain Med*. 2015;16 (Suppl 1):S32–S36. doi: 10.1111/pme.12914. PMID: 26461074
29. Bespalov A, Muller R, Relo AL, Hudzik T. Drug tolerance: a known unknown in translational neuroscience. *Trends Pharmacol Sci*. 2016;37(5):364–378. doi: 10.1016/j.tips.2016.01.008. PMID: 26935643
30. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. *Clin J Pain*. 2008;24:469–478. doi: 10.1097/AJP.0b013e31816b2f26. PMID: 18574357
31. Raffa RB, Pergolizzi JV Jr. Opioid-induced hyperalgesia: is it clinically relevant for the treatment of pain patients? *Pain Manag Nurs*. 2013;14:e67–e83. doi: 10.1016/j.pmn.2011.04.002. PMID: 23972873
32. Volkow ND, McLellan AT. Opioid abuse in chronic pain–misconceptions and mitigation strategies. *N Engl J Med*. 2016;374:1253–1263. doi: 10.1056/NEJMra1507771. PMID: 27028915
33. Miguez G, Laborda MA, Miller RR. Classical conditioning and pain: conditioned analgesia and hyperalgesia. *Acta Psychol (Amst)*. 2014;145:10–20. doi: 10.1016/j.actpsy.2013.10.009. PMID: 24269884
34. Kalant H. Research on tolerance: what can we learn from history? *Alcohol Clin Exp Res*. 1998;22:67–76. PMID: 9514287
35. Satel SL, Kosten TR, Schuckit MA, Fischman MW. Should protracted withdrawal from drugs be included in DSM-IV? *Am J Psychiatry*. 1993;150:695–704. doi: 10.1176/ajp.150.5.695. PMID: 8097618
36. Heilig M, Egli M, Crabbe JC, Becker HC. Acute withdrawal, protracted abstinence and negative affect in alcoholism: are they linked? *Addict Biol*. 2010;15:169–184. doi: 10.1111/j.1369-1600.2009.00194.x. PMID: 20148778
37. Solomon RL. The opponent-process theory of acquired motivation: the costs of pleasure and the benefits of pain. *Am Psychol*. 1980;35:691–712. doi: 10.1037/0003-066X.35.8.691. PMID: 7416563
38. Shurman J, Koob GF, Gutstein HB. Opioids, pain, the brain, and hyperkatifeia: a framework for the rational use of opioids for pain. *Pain Med*. 2010;11:1092–1098. doi: 10.1111/j.1526-4637.2010.00881.x. PMID: 20545871
39. White JM. Pleasure into pain: the consequences of long-term opioid use. *Addict Behav*. 2004;29:1311–1324. doi: 10.1016/j.addbeh.2004.06.007. PMID: 15345267
40. Arout CA, Edens E, Petrakis IL, Sofuoglu M. Targeting opioid-induced hyperalgesia in clinical treatment: neurobiological considerations. *CNS Drugs*. 2015;29:465–486. doi: 10.1007/s40263-015-0255-x. PMID: 26142224
41. Koob GF, Buck CL, Cohen A, et al. Addiction as a stress surfeit disorder. *Neuropharmacology*. 2014;76(Pt B):370–382. doi: 10.1016/j.neuropharm.2013.05.024. PMID: 23747571
42. Ballantyne JC, Stannard C. New addiction criteria: diagnostic challenges persist in treating pain with opioids. *Pain Clinical Updates*. 2013;1:21(5):1–7. Accessed online at https://www.iasp-pain.org/files/FileDownloads/PCU_21-5_web.pdf on 9/3/2017.
43. Substance Abuse and Mental Health Services Administration. Protracted withdrawal. *Subst Abuse Treat Advis*. 2010;9(1):1–8.
44. Kertesz SG. Turning the tide or riptide? The changing opioid epidemic. *Subst Abus*. 2017;38:3–8. doi: 10.1080/08897077.2016.1261070. PMID: 27858590
45. Berland DW, Malinoff HL, Weiner MA, Przybylski R. When opioids fail in chronic pain management: the role for buprenorphine and hospitalization. *Am J Ther*. 2013;20:316–321. doi: 10.1097/MJT.0b013e31827ab599. PMID: 23584313
46. Butler S. Buprenorphine—clinically useful but often misunderstood. *Scand J Pain*. 2013;4:148–152. doi: 10.1016/j.sjpain.2013.05.004.
47. Foster B, Twycross R, Mihalyo M, Wilcock A. Buprenorphine. *J Pain Symptom Manage*. 2013;45:939–949. doi: 10.1016/j.jpainsymman.2013.03.001. PMID: 23648060
48. Johnson RE, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. *J Pain Symptom Manage*. 2005;29:297–326. doi: 10.1016/j.jpainsymman.2004.07.005. PMID: 15781180
49. Rhodin A, Gronbladh L, Nilsson LH, Gordh T. Methadone treatment of chronic non-malignant pain and opioid dependence—a long-term follow-up. *Eur J Pain*. 2006;10:271–278. doi: 10.1016/j.ejpain.2005.05.003. PMID: 15972261
50. Neumann AM, Blondell RD, Jaanimagi U, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. *J Addict Dis*. 2013;32:68–78. doi: 10.1080/10550887.2012.759872. PMID: 23480249
51. Heit HA, Covington E, Good PM. Dear DEA. *Pain Med*. 2004;5:303–308. doi: 10.1111/j.1526-4637.2004.04044.x. PMID: 15367311
52. Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration. *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. CSAT Treatment Improvement Protocols*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004.
53. The Management of Opioid Therapy for Chronic Pain Working Group, Department of Veteran Affairs and Department of Defense: VA/DoD Clinical Practice Guideline Management of Opioid Therapy for Chronic Pain. 2010. Pages 83–89. Accessed online at https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf on 9/3/17.
54. Blondell RD, Ashrafioun L, Dambra CM, Foschio EM, Zielinski AL, Salcedo DM. A clinical trial comparing tapering doses of buprenorphine with steady doses for chronic pain and co-existent opioid addiction. *J Addict Med*. 2010;4:140–146. doi: 10.1097/ADM.0b013e3181ba895d. PMID: 20959867
55. Berna C, Kulich RJ, Rathmell JP. Tapering long-term opioid therapy in chronic noncancer pain: evidence and recommendations for everyday practice. *Mayo Clin Proc*. 2015;90:828–842. doi: 10.1016/j.mayocp.2015.04.003. PMID: 26046416

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Sent: Saturday, December 30, 2017 7:36 AM
To: Brown, David (DHP); Harp, William L. (DHP)
Subject: Buprenorphine mono product use rates Attachment from My EndNote Library
Attachments: Morgan-2017-Injectable naltrexone, oral naltre.pdf

Hello Dr. Brown and Dr. Harp:
Hope you are having a great holidays. I came across a reference that gives some insight into the national use rates of buprenorphine mono product that may be useful for you (8.8% nationally).
Happy New Year

Ajay

FYI: I am steadily progressing on developing a curriculum for residents and professionals regarding severe disabling chronic pain detailing the neurobiology, its evolution and treatment approach. I use a narrative approach and this is very successful with my patients. But, it is a whole different challenge to educate professionals with entrenched ideas. We will have something ready hopefully in the next few months

Reference Type: Journal Article
Record Number: 3220
Author: Morgan, J. R., Schackman, B. R., Leff, J. A., Linas, B. P. and Walley, A. Y.
Year: 2017
Title: Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population
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Short Title: Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population
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Abstract: We investigated prescribing patterns for four opioid use disorder (OUD) medications: 1) injectable naltrexone, 2) oral naltrexone, 3) sublingual or oralmucosal buprenorphine/naloxone, and 4) sublingual buprenorphine as well as transdermal buprenorphine (which is approved for treating pain, but not OUD) in a nationally representative claims-based database (Truven Health MarketScan(R)) of commercially insured individuals in the United States. We calculated the prevalence of OUD in the database for each year from 2010 to 2014 and the proportion of diagnosed patient months on OUD medication. We compared characteristics of individuals diagnosed with OUD who did and did not receive these medications with bivariate descriptive statistics. Finally, we fit a Cox proportional hazards model of time to discontinuation of therapy as a function of therapy type,

controlling for relevant confounders. From 2010 to 2014, the proportion of commercially insured individuals diagnosed with OUD grew by fourfold (0.12% to 0.48%), but the proportion of diagnosed patient-months on medication decreased from 25% in 2010 (0.05% injectable naltrexone, 0.4% oral naltrexone, 23.1% sublingual or oralmucosal buprenorphine/naloxone, 1.5% sublingual buprenorphine, and 0% transdermal buprenorphine) to 16% in 2014 (0.2% injectable naltrexone, 0.4% oral naltrexone, 13.8% sublingual or oralmucosal buprenorphine/naloxone, 1.4% sublingual buprenorphine, and 0.3% transdermal buprenorphine). Individuals who received medication therapy were more likely to be male, younger, and have an additional substance use disorder compared with those diagnosed with OUD who did not receive medication therapy. Those prescribed injectable naltrexone were more often male, younger, and diagnosed with additional substance use disorders compared with those prescribed other medications for opioid use disorder (MOUDs). At 30 days after initiation, 52% for individuals treated with injectable naltrexone, 70% for individuals treated with oral naltrexone, 31% for individuals treated with sublingual or oralmucosal buprenorphine/naloxone, 58% for individuals treated with sublingual buprenorphine, and 51% for individuals treated with transdermal buprenorphine discontinued treatment. In the Cox proportional hazard model, use of injectable naltrexone, oral naltrexone, sublingual buprenorphine, and transdermal buprenorphine were all associated with significantly greater hazard of discontinuing therapy beginning >30days after MOUD initiation (HR=2.17, 2.54, 1.15, and 2.21, respectively, 95% CIs 2.04-2.30, 2.45-2.64, 1.10-1.19, and 2.11-2.33), compared with the use of sublingual or oralmucosal buprenorphine/naloxone. This analysis demonstrates that the use of evidence-based medication therapies has not kept pace with increases in OUD diagnoses in commercially insured populations in the United States. Among those who have been treated, discontinuation rates >30days after initiation are high. The proportion treated with injectable naltrexone, oral naltrexone, and transdermal buprenorphine grew over time but remains small, and the discontinuation rates are higher among those treated with these medications compared with those treated with sublingual or oralmucosal buprenorphine/naloxone. In the face of the opioid overdose and addiction crisis, new efforts are needed at the provider, health system, and policy levels so that MOUD availability and uptake keep pace with new OUD diagnoses and OUD treatment discontinuation is minimized.

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

Recommendations and Reports / March 18, 2016 / 65(1);1–49

On March 15, 2016, this report was posted online as an MMWR Early Release.

Please note: *An erratum has been published for this report. To view the erratum, please click here.*

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View suggested citation and related materials

Summary

This guideline provides recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses 1) when to initiate or continue opioids for chronic pain; 2) opioid selection, dosage, duration, follow-up, and discontinuation; and 3) assessing risk and addressing harms of opioid use. CDC developed the guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, and recommendations are made on the basis of a systematic review of the scientific evidence while considering benefits and harms, values and preferences, and resource allocation. CDC obtained input from experts, stakeholders, the public, peer reviewers, and a federally chartered advisory committee. It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. This guideline is intended to improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death. CDC has provided a checklist for prescribing opioids for chronic pain (http://stacks.cdc.gov/view/cdc/38025 (http://stacks.cdc.gov/view/cdc/38025)) as well as a website (http://www.cdc.gov/drugoverdose/prescribingresources.html (http://www.cdc.gov/drugoverdose/prescribing/resources.html)) with additional tools to guide clinicians in implementing the recommendations.

Introduction

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Background

Opioids are commonly prescribed for pain. An estimated 20% of patients presenting to physician offices with noncancer pain symptoms or pain-related diagnoses (including acute and chronic pain) receive an opioid prescription (*1*). In 2012, health care providers wrote 259 million prescriptions for opioid pain medication, enough for every adult in the United States to have a bottle of pills (*2*). Opioid prescriptions per capita increased 7.3% from 2007 to 2012, with opioid prescribing rates increasing more for family practice, general practice, and internal medicine compared with other specialties (*3*). Rates of opioid prescribing vary greatly across states in ways that cannot be explained by the underlying health status of the population, highlighting the lack of consensus among clinicians on how to use opioid pain medication (*2*).

Prevention, assessment, and treatment of chronic pain are challenges for health providers and systems. Pain might go unrecognized, and patients, particularly members of racial and ethnic minority groups, women, the elderly, persons with cognitive impairment, and those with cancer and at the end of life, can be at risk for inadequate pain treatment (*4*). Patients can experience persistent pain that is not well controlled. There are clinical, psychological, and social consequences associated with chronic pain including limitations in complex activities, lost work productivity, reduced quality of life, and stigma, emphasizing the importance of appropriate and compassionate patient care (*4*). Patients should receive appropriate pain treatment based on a careful consideration of the benefits and risks of treatment options.

Chronic pain has been variably defined but is defined within this guideline as pain that typically lasts >3 months or past the time of normal tissue healing (*5*). Chronic pain can be the result of an underlying medical disease or condition, injury, medical treatment, inflammation, or an unknown cause (*4*). Estimates of the prevalence of chronic pain vary, but it is clear that the number of persons experiencing chronic pain in the United States is substantial. The 1999–2002 National Health and Nutrition Examination Survey estimated that 14.6% of adults have current widespread or localized pain lasting at least 3 months (*6*). Based on a survey conducted during 2001–2003 (*7*), the overall prevalence of common, predominantly musculoskeletal pain conditions (e.g., arthritis, rheumatism, chronic back or neck problems, and frequent severe headaches) was estimated at 43% among adults in the United States, although minimum duration of symptoms was not specified. Most recently, analysis of data from the 2012 National Health Interview Study showed that 11.2% of adults report having daily pain (*8*). Clinicians should consider the full range of therapeutic options for the treatment of chronic pain. However, it is hard to estimate the number of persons who could potentially benefit from opioid pain medication long term. Evidence supports short-term efficacy of opioids for reducing pain and improving function in noncancer nociceptive and neuropathic pain in randomized clinical trials lasting primarily ≤12 weeks (*9,10*), and patients receiving opioid therapy for chronic pain report some pain relief when surveyed (*11–13*). However, few studies have been conducted to rigorously assess the long-term

benefits of opioids for chronic pain (pain lasting >3 months) with outcomes examined at least 1 year later (*14*). On the basis of data available from health systems, researchers estimate that 9.6–11.5 million adults, or approximately 3%–4% of the adult U.S. population, were prescribed long-term opioid therapy in 2005 (*15*).

Opioid pain medication use presents serious risks, including overdose and opioid use disorder. From 1999 to 2014, more than 165,000 persons died from overdose related to opioid pain medication in the United States (*16*). In the past decade, while the death rates for the top leading causes of death such as heart disease and cancer have decreased substantially, the death rate associated with opioid pain medication has increased markedly (*17*). Sales of opioid pain medication have increased in parallel with opioid-related overdose deaths (*18*). The Drug Abuse Warning Network estimated that >420,000 emergency department visits were related to the misuse or abuse of narcotic pain relievers in 2011, the most recent year for which data are available (*19*). Although clinical criteria have varied over time, opioid use disorder is a problematic pattern of opioid use leading to clinically significant impairment or distress. This disorder is manifested by specific criteria such as unsuccessful efforts to cut down or control use and use resulting in social problems and a failure to fulfill major role obligations at work, school, or home (*20*). This diagnosis has also been referred to as "abuse or dependence" and "addiction" in the literature, and is different from tolerance (diminished response to a drug with repeated use) and physical dependence (adaptation to a drug that produces symptoms of withdrawal when the drug is stopped), both of which can exist without a diagnosed disorder. In 2013, on the basis of DSM-IV diagnosis criteria, an estimated 1.9 million persons abused or were dependent on prescription opioid pain medication (*21*). Having a history of a prescription for an opioid pain medication increases the risk for overdose and opioid use disorder (*22–24*), highlighting the value of guidance on safer prescribing practices for clinicians. For example, a recent study of patients aged 15–64 years receiving opioids for chronic noncancer pain and followed for up to 13 years revealed that one in 550 patients died from opioid-related overdose at a median of 2.6 years from their first opioid prescription, and one in 32 patients who escalated to opioid dosages >200 morphine milligram equivalents (MME) died from opioid-related overdose (*25*).

This guideline provides recommendations for the prescribing of opioid pain medication by primary care clinicians for chronic pain (i.e., pain conditions that typically last >3 months or past the time of normal tissue healing) in outpatient settings outside of active cancer treatment, palliative care, and end-of-life care. Although the guideline does not focus broadly on pain management, appropriate use of long-term opioid therapy must be considered within the context of all pain management strategies (including nonopioid pain medications and nonpharmacologic treatments). CDC's recommendations are made on the basis of a systematic review of the best available evidence, along with input from experts, and further review and deliberation by a federally chartered advisory committee. The guideline is intended to ensure that clinicians and patients consider safer and more effective treatment, improve patient outcomes such as reduced pain and improved function, and reduce the number of persons who develop opioid use disorder, overdose, or experience other adverse events related to these drugs. Clinical decision making should be based on a relationship between the clinician and patient, and an understanding of the patient's clinical situation, functioning, and life context. The recommendations in the guideline are voluntary, rather than prescriptive standards. They are based on emerging evidence, including observational studies or randomized clinical trials with notable limitations. Clinicians should consider the circumstances and unique needs of each patient when providing care.

Rationale

Primary care clinicians report having concerns about opioid pain medication misuse, find managing patients with chronic pain stressful, express concern about patient addiction, and report insufficient training in prescribing opioids (*26*). Across specialties, physicians believe that opioid pain medication can be effective in controlling pain, that addiction is a common consequence of prolonged use, and that long-term opioid therapy often is overprescribed for patients with chronic noncancer pain (*27*). These attitudes and beliefs, combined with increasing trends in opioid-related overdose, underscore the need for better clinician guidance on opioid prescribing. Clinical practice guidelines focused on prescribing can improve clinician knowledge, change prescribing practices (*28*), and ultimately benefit patient health.

Professional organizations, states, and federal agencies (e.g., the American Pain Society/American Academy of Pain Medicine, 2009; the Washington Agency Medical Directors Group, 2015; and the U.S. Department of Veterans Affairs/Department of Defense, 2010) have developed guidelines for opioid prescribing (*29–31*). Existing guidelines share some common elements, including dosing thresholds, cautious titration, and risk mitigation strategies such as using risk assessment tools, treatment agreements, and urine drug testing. However, there is considerable variability in the specific recommendations (e.g., range of dosing thresholds of 90 MME/day to 200 MME/day), audience (e.g., primary care clinicians versus specialists), use of evidence (e.g., systematic review, grading of evidence and recommendations, and role of expert opinion), and rigor of methods for addressing conflict of interest (*32*). Most guidelines, especially those that are not based on evidence from scientific studies published in 2010 or later, also do not reflect the most recent scientific evidence about risks related to opioid dosage.

This CDC guideline offers clarity on recommendations based on the most recent scientific evidence, informed by expert opinion and stakeholder and public input. Scientific research has identified high-risk prescribing practices that have contributed to the overdose epidemic (e.g., high-dose prescribing, overlapping opioid and benzodiazepine prescriptions, and extended-release/long-acting [ER/LA] opioids for acute pain) (*24,33,34*). Using guidelines to address problematic prescribing has the potential to optimize care and improve patient safety based on evidence-based practice (*28*), as well as reverse the cycle of opioid pain medication misuse that contributes to the opioid overdose epidemic.

Scope and Audience

This guideline is intended for primary care clinicians (e.g., family physicians and internists) who are treating patients with chronic pain (i.e., pain lasting >3 months or past the time of normal tissue healing) in outpatient settings. Prescriptions by primary care clinicians account for nearly half of all dispensed opioid prescriptions, and the growth in prescribing rates among these clinicians has been above average (*3*). Primary care clinicians include physicians as well as nurse practitioners and physician assistants. Although the focus is on primary care clinicians, because clinicians work within team-based care, the recommendations refer to and promote integrated pain management and collaborative working relationships with other providers (e.g., behavioral health

providers, pharmacists, and pain management specialists). Although the transition from use of opioid therapy for acute pain to use for chronic pain is hard to predict and identify, the guideline is intended to inform clinicians who are considering prescribing opioid pain medication for painful conditions that can or have become chronic.

This guideline is intended to apply to patients aged ≥18 years with chronic pain outside of palliative and end-of-life care. For this guideline, palliative care is defined in a manner consistent with that of the Institute of Medicine as care that provides relief from pain and other symptoms, supports quality of life, and is focused on patients with serious advanced illness. Palliative care can begin early in the course of treatment for any serious illness that requires excellent management of pain or other distressing symptoms (*35*). End-of-life care is defined as care for persons with a terminal illness or at high risk for dying in the near future in hospice care, hospitals, long-term care settings, or at home. Patients within the scope of this guideline include cancer survivors with chronic pain who have completed cancer treatment, are in clinical remission, and are under cancer surveillance only. The guideline is not intended for patients undergoing active cancer treatment, palliative care, or end-of-life care because of the unique therapeutic goals, ethical considerations, opportunities for medical supervision, and balance of risks and benefits with opioid therapy in such care.

The recommendations address the use of opioid pain medication in certain special populations (e.g., older adults and pregnant women) and in populations with conditions posing special risks (e.g., a history of substance use disorder). The recommendations do not address the use of opioid pain medication in children or adolescents aged <18 years. The available evidence concerning the benefits and harms of long-term opioid therapy in children and adolescents is limited, and few opioid medications provide information on the label regarding safety and effectiveness in pediatric patients. However, observational research shows significant increases in opioid prescriptions for pediatric populations from 2001 to 2010 (*36*), and a large proportion of adolescents are commonly prescribed opioid pain medications for conditions such as headache and sports injuries (e.g., in one study, 50% of adolescents presenting with headache received a prescription for an opioid pain medication) (*37,38*). Adolescents who misuse opioid pain medication often misuse medications from their own previous prescriptions (*39*), with an estimated 20% of adolescents with currently prescribed opioid medications reporting using them intentionally to get high or increase the effects of alcohol or other drugs (*40*). Use of prescribed opioid pain medication before high school graduation is associated with a 33% increase in the risk of later opioid misuse (*41*). Misuse of opioid pain medications in adolescence strongly predicts later onset of heroin use (*42*). Thus, risk of opioid medication use in pediatric populations is of great concern. Additional clinical trial and observational research is needed, and encouraged, to inform development of future guidelines for this critical population.

The recommendations are not intended to provide guidance on use of opioids as part of medication-assisted treatment for opioid use disorder. Some of the recommendations might be relevant for acute care settings or other specialists, such as emergency physicians or dentists, but use in these settings or by other specialists is not the focus of this guideline. Readers are referred to other sources for prescribing recommendations within acute care settings and in dental practice, such as the American College of Emergency Physicians' guideline for prescribing of opioids in the emergency department (*43*); the American Society of Anesthesiologists' guideline for acute pain management in the perioperative setting (*44*); the Washington Agency Medical Directors' Group Interagency Guideline on Prescribing Opioids for Pain, Part II: Prescribing Opioids in the Acute and Subacute Phase (*30*); and the Pennsylvania Guidelines on the Use of Opioids in Dental Practice (*45*). In addition, given the challenges of managing the painful complications of sickle cell disease, readers are referred to the NIH National Heart, Lung, and Blood Institute's Evidence Based Management of Sickle Cell Disease Expert Panel Report for management of sickle cell disease (*46*).

Guideline Development Methods

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Guideline Development Using the Grading of Recommendations Assessment, Development, and Evaluation Method

CDC developed this guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (http://www.gradeworkinggroup.org (http://www.gradeworkinggroup.org)). This method specifies the systematic review of scientific evidence and offers a transparent approach to grading quality of evidence and strength of recommendations. The method has been adapted by the CDC Advisory Committee on Immunization Practices (ACIP) (*47*). CDC has applied the ACIP translation of the GRADE framework in this guideline. Within the ACIP GRADE framework, the body of evidence is categorized in a hierarchy. This hierarchy reflects degree of confidence in the effect of a clinical action on health outcomes. The categories include 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). Type of evidence is categorized by study design as well as 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 a constellation of plausible biases that could change observations of effects. Type 1 evidence indicates that one can be very confident that the true effect lies close to that of 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 a possibility that it is substantially different; type 3 evidence means that confidence in the effect estimate is limited and the true effect might be substantially different from the estimate of the effect; and type 4 evidence indicates that one has very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of the effect (*47,48*). When no studies are present, evidence is considered to be insufficient. The ACIP GRADE framework places recommendations in two categories, Category A and Category B. Four major factors determine the category of the recommendation: the quality of evidence, the balance between desirable and undesirable effects, values and preferences, and resource allocation (cost). Category A recommendations apply to all persons in a specified group and indicate that most patients should receive the recommended course of action. Category B recommendations indicate that there should be individual decision making; different choices will be appropriate for different patients, so clinicians must help patients arrive at a decision consistent with patient values and preferences, and specific clinical situations (*47*). According to the GRADE methodology, a particular quality of evidence does not necessarily imply a particular strength of recommendation (*48–50*). Category A recommendations can be made based on type 3 or type 4 evidence when the advantages of a clinical action greatly outweigh the disadvantages based on a consideration of benefits and harms, values and preferences, and costs. Category B recommendations are made when the advantages and disadvantages of a clinical action are more balanced. GRADE methodology is

discussed extensively elsewhere (*47*,*51*). The U.S. Preventive Services Task Force (USPSTF) follows different methods for developing and categorizing recommendations (http://www.uspreventiveservicestaskforce.org (http://www.uspreventiveservicestaskforce.org)). USPSTF recommendations focus on preventive services and are categorized as A, B, C, D, and I. Under the Affordable Care Act, all "nongrandfathered" health plans (that is, those health plans not in existence prior to March 23, 2010 or those with significant changes to their coverage) and expanded Medicaid plans are required to cover preventive services recommended by USPSTF with a category A or B rating with no cost sharing. The coverage requirements went into effect September 23, 2010. Similar requirements are in place for vaccinations recommended by ACIP, but do not exist for other recommendations made by CDC, including recommendations within this guideline.

A previously published systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ) on the effectiveness and risks of long-term opioid treatment of chronic pain (*14*,*52*) initially served to directly inform the recommendation statements. This systematic clinical evidence review addressed the effectiveness of long-term opioid therapy for outcomes related to pain, function, and quality of life; the comparative effectiveness of different methods for initiating and titrating opioids; the harms and adverse events associated with opioids; and the accuracy of risk-prediction instruments and effectiveness of risk mitigation strategies on outcomes related to overdose, addiction, abuse, or misuse. For the current guideline development, CDC conducted additional literature searches to update the evidence review to include more recently available publications and to answer an additional clinical question about the effect of opioid therapy for acute pain on long-term use. More details about the literature search strategies and GRADE methods applied are provided in the Clinical Evidence Review (http://stacks.cdc.gov/view/cdc/38026 (http://stacks.cdc.gov/view/cdc/38026)). CDC developed GRADE evidence tables to illustrate the quality of the evidence for each clinical question.

As identified in the AHRQ-sponsored clinical evidence review, the overall evidence base for the effectiveness and risks of long-term opioid therapy is low in quality per the GRADE criteria. Thus, contextual evidence is needed to provide information about the benefits and harms of nonpharmacologic and nonopioid pharmacologic therapy and the epidemiology of opioid pain medication overdose and inform the recommendations. Further, as elucidated by the GRADE Working Group, supplemental information on clinician and patient values and preferences and resource allocation can inform judgments of benefits and harms and be helpful for translating the evidence into recommendations. CDC conducted a contextual evidence review to supplement the clinical evidence review based on systematic searches of the literature. The review focused on the following four areas: effectiveness of nonpharmacologic and nonopioid pharmacologic treatments; benefits and harms related to opioid therapy (including additional studies not included in the clinical evidence review such as studies that evaluated outcomes at any duration or used observational study designs related to specific opioid pain medications, high-dose opioid therapy, co-prescription of opioids with other controlled substances, duration of opioid use, special populations, risk stratification/mitigation approaches, and effectiveness of treatments for addressing potential harms of opioid therapy); clinician and patient values and preferences; and resource allocation. CDC constructed narrative summaries of this contextual evidence and used the information to support the clinical recommendations. More details on methods for the contextual evidence review are provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/cdc/38027 (http://stacks.cdc.gov/view/cdc/38027)).

On the basis of a review of the clinical and contextual evidence (review methods are described in more detail in subsequent sections of this report), CDC drafted recommendation statements focused on determining when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. To help assure the draft guideline's integrity and credibility, CDC then began a multistep review process to obtain input from experts, stakeholders, and the public to help refine the recommendations.

Solicitation of Expert Opinion

CDC sought the input of experts to assist in reviewing the evidence and providing perspective on how CDC used the evidence to develop the draft recommendations. These experts, referred to as the "Core Expert Group" (CEG) included subject matter experts, representatives of primary care professional societies and state agencies, and an expert in guideline development methodology.* CDC identified subject matter experts with high scientific standing; appropriate academic and clinical training and relevant clinical experience; and proven scientific excellence in opioid prescribing, substance use disorder treatment, and pain management. CDC identified representatives from leading primary care professional organizations to represent the audience for this guideline. Finally, CDC identified state agency officials and representatives based on their experience with state guidelines for opioid prescribing that were developed with multiple agency stakeholders and informed by scientific literature and existing evidence-based guidelines.

Prior to their participation, CDC asked potential experts to reveal possible conflicts of interest such as financial relationships with industry, intellectual preconceptions, or previously stated public positions. Experts could not serve if they had conflicts that might have a direct and predictable effect on the recommendations. CDC excluded experts who had a financial or promotional relationship with a company that makes a product that might be affected by the guideline. CDC reviewed potential nonfinancial conflicts carefully (e.g., intellectual property, travel, public statements or positions such as congressional testimony) to determine if the activities would have a direct and predictable effect on the recommendations. CDC determined the risk of these types of activities to be minimal for the identified experts. All experts completed a statement certifying that there was no potential or actual conflict of interest. Activities that did not pose a conflict (e.g., participation in Food and Drug Administration [FDA] activities or other guideline efforts) are disclosed.

CDC provided to each expert written summaries of the scientific evidence (both the clinical and contextual evidence reviews conducted for this guideline) and CDC's draft recommendation statements. Experts provided individual ratings for each draft recommendation statement based on the balance of benefits and harms, evidence strength, certainty of values and preferences, cost, recommendation strength, rationale, importance, clarity, and ease of implementation. CDC hosted an in-person meeting of the experts that was held on June 23–24, 2015, in Atlanta, Georgia, to seek their views on the evidence and draft recommendations and to better understand their premeeting ratings. CDC sought the experts' individual opinions at the meeting. Although there was widespread agreement on some of the recommendations, there was disagreement on others. Experts did not vote on the recommendations or seek to come to a consensus. Decisions about recommendations to be included in the guideline, and their rationale, were made by CDC. After revising the guideline, CDC sent written copies of it to each of the experts for review and asked for any additional comments; CDC reviewed these written comments and considered them when making further revisions to the draft guideline. The experts have not reviewed the final version of the guideline.

Federal Partner Engagement

Given the scope of this guideline and the interest of agencies across the federal government in appropriate pain management, opioid prescribing, and related outcomes, CDC invited its National Institute of Occupational Safety and Health and CDC's federal partners to observe the expert meeting, provide written comments on the full draft guideline after the meeting, and review the guideline through an agency clearance process; CDC reviewed comments and incorporated changes. Interagency collaboration will be critical for translating these recommendations into clinical practice. Federal partners included representatives from the Substance Abuse and Mental Health Services Administration, the National Institute on Drug Abuse, FDA, the U.S. Department of Veterans Affairs, the U.S. Department of Defense, the Office of the National Coordinator for Health Information Technology, the Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, AHRQ, and the Office of National Drug Control Policy.

Stakeholder Comment

Given the importance of the guideline for a wide variety of stakeholders, CDC also invited review from a Stakeholder Review Group (SRG) to provide comment so that CDC could consider modifications that would improve the recommendations' specificity, applicability, and ease of implementation. The SRG included representatives from professional organizations that represent specialties that commonly prescribe opioids (e.g., pain medicine, physical medicine and rehabilitation), delivery systems within which opioid prescribing occurs (e.g., hospitals), and representation from community organizations with interests in pain management and opioid prescribing.* Representatives from each of the SRG organizations were provided a copy of the guideline for comment. Each of these representatives provided written comments. Once input was received from the full SRG, CDC reviewed all comments and carefully considered them when revising the draft guideline.

Constituent Engagement

To obtain initial perspectives from constituents on the recommendation statements, including clinicians and prospective patients, CDC convened a constituent engagement webinar and circulated information about the webinar in advance through announcements to partners. CDC hosted the webinar on September 16 and 17, 2015, provided information about the methodology for developing the guideline, and presented the key recommendations. A fact sheet was posted on the CDC Injury Center website (http://www.cdc.gov/injury (http://www.cdc.gov/injury)) summarizing the guideline development process and clinical practice areas addressed in the guideline; instructions were included on how to submit comments via email. CDC received comments during and for 2 days following the first webinar. Over 1,200 constituent comments were received. Comments were reviewed and carefully considered when revising the draft guideline.

Peer Review

Per the final information quality bulletin for peer review (https://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2005/m05-03.pdf (https://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2005/m05-03.pdf)), peer review requirements applied to this guideline because it provides influential scientific information that could have a clear and substantial impact on public- and private-sector decisions. Three experts independently reviewed the guideline to determine the reasonableness and strength of recommendations; the clarity with which scientific uncertainties were clearly identified; and the rationale, importance, clarity, and ease of implementation of the recommendations.* CDC selected peer reviewers based on expertise, diversity of scientific viewpoints, and independence from the guideline development process. CDC assessed and managed potential conflicts of interest using a process similar to the one as described for solicitation of expert opinion. No financial interests were identified in the disclosure and review process, and nonfinancial activities were determined to be of minimal risk; thus, no significant conflict of interest concerns were identified. CDC placed the names of peer reviewers on the CDC and the National Center for Injury Prevention and Control Peer Review Agenda websites that are used to provide information about the peer review of influential documents. CDC reviewed peer review comments and revised the draft guideline accordingly.

Public Comment

To obtain comments from the public on the full guideline, CDC published a notice in the *Federal Register* (80 FR 77351) announcing the availability of the guideline and the supporting clinical and contextual evidence reviews for public comment. The comment period closed January 13, 2016. CDC received more than 4,350 comments from the general public, including patients with chronic pain, clinicians, families who have lost loved ones to overdose, medical associations, professional organizations, academic institutions, state and local governments, and industry. CDC reviewed each of the comments and carefully considered them when revising the draft guideline.

Federal Advisory Committee Review and Recommendation

The National Center for Injury Prevention and Control (NCIPC) Board of Scientific Counselors (BSC) is a federal advisory committee that advises and makes recommendations to the Secretary of the Department of Health and Human Services, the Director of CDC, and the Director of NCIPC.* The BSC makes recommendations regarding policies, strategies, objectives, and priorities, and reviews progress toward injury and violence prevention. CDC sought the BSC's advice on the draft guideline. BSC members are special government employees appointed as CDC advisory committee members; as such, all members completed an OGE Form 450 to disclose relevant interests. BSC members also reported on their disclosures during meetings. Disclosures for the BSC are reported in the guideline.

To assist in guideline review, on December 14, 2015, via Federal Register notice, CDC announced the intent to form an Opioid Guideline Workgroup (OGW) to provide observations on the draft guideline to the BSC. CDC provided the BSC with the draft guideline as well as summaries of comments provided to CDC by stakeholders, constituents, and peer reviewers, and edits made to the draft guideline in response. During an open meeting held on January 7, 2016, the BSC recommended the formation of the OGW. The OGW included a balance of perspectives from audiences directly affected by the guideline, audiences that would be directly involved with implementing the recommendations, and audiences qualified to provide representation. The OGW comprised clinicians, subject matter experts, and a patient representative, with the following perspectives represented: primary care, pain medicine, public health, behavioral health, substance abuse treatment, pharmacy, patients, and research.* Additional sought-after attributes were appropriate academic and clinical training and relevant

clinical experience; high scientific standing; and knowledge of the patient, clinician, and caregiver perspectives. In accordance with CDC policy, two BSC committee members also served as OGW members, with one serving as the OGW Chair. The professional credentials and interests of OGW members were carefully reviewed to identify possible conflicts of interest such as financial relationships with industry, intellectual preconceptions, or previously stated public positions. Only OGW members whose interests were determined to be minimal were selected. When an activity was perceived as having the potential to affect a specific aspect of the recommendations, the activity was disclosed, and the OGW member was recused from discussions related to that specific aspect of the recommendations (e.g., urine drug testing and abuse-deterrent formulations). Disclosures for the OGW are reported. CDC and the OGW identified ad-hoc consultants to supplement the workgroup expertise, when needed, in the areas of pediatrics, occupational medicine, obstetrics and gynecology, medical ethics, addiction psychiatry, physical medicine and rehabilitation, guideline development methodology, and the perspective of a family member who lost a loved one to opioid use disorder or overdose.

The BSC charged the OGW with reviewing the quality of the clinical and contextual evidence reviews and reviewing each of the recommendation statements and accompanying rationales. For each recommendation statement, the OGW considered the quality of the evidence, the balance of benefits and risks, the values and preferences of clinicians and patients, the cost feasibility, and the category designation of the recommendation (A or B). The OGW also reviewed supplementary documents, including input provided by the CEG, SRG, peer reviewers, and the public. OGW members discussed the guideline accordingly during virtual meetings and drafted a summary report of members' observations, including points of agreement and disagreement, and delivered the report to the BSC.

NCIPC announced an open meeting of the NCIPC BSC in the Federal Register on January 11, 2015. The BSC met on January 28, 2016, to discuss the OGW report and deliberate on the draft guideline itself. Members of the public provided comments at this meeting. After discussing the OGW report, deliberating on specific issues about the draft guideline identified at the meeting, and hearing public comment, the BSC voted unanimously: to support the observations made by the OGW; that CDC adopt the guideline recommendations that, according to the workgroup's report, had unanimous or majority support; and that CDC further consider the guideline recommendations for which the group had mixed opinions. CDC carefully considered the OGW observations, public comments, and BSC recommendations, and revised the guideline in response.

Summary of the Clinical Evidence Review

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Primary Clinical Questions

CDC conducted a clinical systematic review of the scientific evidence to identify the effectiveness, benefits, and harms of long-term opioid therapy for chronic pain, consistent with the GRADE approach (*47*,*48*). Long-term opioid therapy is defined as use of opioids on most days for >3 months. A previously published AHRQ-funded systematic review on the effectiveness and risks of long-term opioid therapy for chronic pain comprehensively addressed four clinical questions (*14*,*52*). CDC, with the assistance of a methodology expert, searched the literature to identify newly published studies on these four original questions. Because long-term opioid use might be affected by use of opioids for acute pain, CDC subsequently developed a fifth clinical question (last in the series below), and in collaboration with a methodologist conducted a systematic review of the scientific evidence to address it. In brief, five clinical questions were addressed

- The effectiveness of long-term opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for long term (≥1 year) outcomes related to pain, function, and quality of life, and how effectiveness varies according to the type/cause of pain, patient demographics, and patient comorbidities (Key Question [KQ] 1).
- The risks of opioids versus placebo or no opioids on abuse, addiction, overdose, and other harms, and how harms vary according to the type/cause of pain, patient demographics, patient comorbidities, and dose (KQ2).
- The comparative effectiveness of opioid dosing strategies (different methods for initiating and titrating opioids; immediate-release versus ER/LA opioids; different ER/LA opioids; immediate- release plus ER/LA opioids versus ER/LA opioids alone; scheduled, continuous versus as-needed dosing; dose escalation versus dose maintenance; opioid rotation versus maintenance; different strategies for treating acute exacerbations of chronic pain; decreasing opioid doses or tapering off versus continuation; and different tapering protocols and strategies) (KQ3).
- The accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse; the effectiveness of risk mitigation strategies (use of risk prediction instruments); effectiveness of risk mitigation strategies including opioid management plans, patient education, urine drug testing, prescription drug monitoring program (PDMP) data, monitoring instruments, monitoring intervals, pill counts, and abuse-deterrent formulations for reducing risk for opioid overdose, addiction, abuse, or misuse; and the comparative effectiveness of treatment strategies for managing patients with addiction (KQ4).
- The effects of prescribing opioid therapy versus not prescribing opioid therapy for acute pain on long-term use (KQ5).

The review was focused on the effectiveness of long-term opioid therapy on long-term (>1 year) outcomes related to pain, function, and quality of life to ensure that findings are relevant to patients with chronic pain and long-term opioid prescribing. The effectiveness of short-term opioid therapy has already been established (*10*). However, opioids have unique effects such as tolerance and physical dependence that might influence assessments of benefit over time. These effects raise questions about whether findings on short-term effectiveness of opioid therapy can be extrapolated to estimate benefits of long-term therapy for chronic pain. Thus, it is important to consider studies that provide data on long-term benefit. For certain opioid-related harms (overdose, fractures, falls, motor vehicle crashes), observational studies were included with outcomes measured at shorter intervals because such outcomes can occur early during opioid therapy, and such harms are not captured well in short-term clinical trials. A detailed listing of the key questions is provided in the Clinical Evidence Review (http://stacks.cdc.gov/view/cdc/38026 (http://stacks.cdc.gov/view/cdc/38026)).

Clinical Evidence Systematic Review Methods

Complete methods and data for the 2014 AHRQ report, upon which this updated systematic review is based, have been published previously (*14*,*52*). Study authors developed the protocol using a standardized process (*53*) with input from experts and the public and registered the protocol in the PROSPERO database (*54*). For the 2014 AHRQ report, a research librarian searched MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane

Database of Systematic Reviews, PsycINFO, and CINAHL for English-language articles published January 2008 through August 2014, using search terms for opioid therapy, specific opioids, chronic pain, and comparative study designs. Also included were relevant studies from an earlier review (*10*) in which searches were conducted without a date restriction, reference lists were reviewed, and ClinicalTrials.gov was searched. CDC updated the AHRQ literature search using the same search strategies as in the original review including studies published before April, 2015. Seven additional studies met inclusion criteria and were added to the review. CDC used the GRADE approach outlined in the ACIP Handbook for Developing Evidence-Based Recommendations (*47*) to rate the quality of evidence for the full body of evidence (evidence from the 2014 AHRQ review plus the update) for each clinical question. Evidence was categorized into the following types: type 1 (randomized clinical trials or overwhelming evidence from observational studies), type 2 (randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies), type 3 (observational studies, or randomized clinical trials with notable limitations), or type 4 (clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations). When no studies were present, evidence was considered to be insufficient. Per GRADE methods, type of evidence was categorized by study design as well as a function of limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, magnitude of treatment effects, dose-response gradient, and constellation of plausible biases that could change effects. Results were synthesized qualitatively, highlighting new evidence identified during the update process. Meta-analysis was not attempted due to the small numbers of studies, variability in study designs and clinical heterogeneity, and methodological shortcomings of the studies. More detailed information about data sources and searches, study selection, data extraction and quality assessment, data synthesis, and update search yield and new evidence for the current review is provided in the Clinical Evidence Review (http://stacks.cdc.gov/view/cdc/38026 (http://stacks.cdc.gov/view/cdc/38026)).

Summary of Findings for Clinical Questions

The main findings of this updated review are consistent with the findings of the 2014 AHRQ report (*14*). In summary, evidence on long-term opioid therapy for chronic pain outside of end-of-life care remains limited, with insufficient evidence to determine long-term benefits versus no opioid therapy, though evidence suggests risk for serious harms that appears to be dose-dependent. These findings supplement findings from a previous review of the effectiveness of opioids for adults with chronic noncancer pain. In this previous review, based on randomized trials predominantly ≤12 weeks in duration, opioids were found to be moderately effective for pain relief, with small benefits for functional outcomes; although estimates vary, based on uncontrolled studies, a high percentage of patients discontinued long-term opioid use because of lack of efficacy and because of adverse events (*10*).

The GRADE evidence summary with type of evidence ratings for the five clinical questions for the current evidence review are outlined (Table 1). This summary is based on studies included in the AHRQ 2014 review (35 studies) plus additional studies identified in the updated search (seven studies). Additional details on findings from the original review are provided in the full 2014 AHRQ report (*14*,*52*). Full details on the clinical evidence review findings supporting this guideline are provided in the Clinical Evidence Review (http://stacks.cdc.gov/view/cdc/38026 (http://stacks.cdc.gov/view/cdc/38026)).

Effectiveness

For KQ1, no study of opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for chronic pain evaluated long-term (≥1 year) outcomes related to pain, function, or quality of life. Most placebo-controlled randomized clinical trials were ≤6 weeks in duration. Thus, the body of evidence for KQ1 is rated as insufficient (0 studies contributing) (*14*).

Harms

For KQ2, the body of evidence is rated as type 3 (12 studies contributing; 11 from the original review plus one new study). One fair-quality cohort study found that long-term opioid therapy is associated with increased risk for an opioid abuse or dependence diagnosis (as defined by ICD-9-CM codes) versus no opioid prescription (*22*). Rates of opioid abuse or dependence diagnosis ranged from 0.7% with lower-dose (≤36 MME) chronic therapy to 6.1% with higher-dose (≥120 MME) chronic therapy, versus 0.004% with no opioids prescribed. Ten fair-quality uncontrolled studies reported estimates of opioid abuse, addiction, and related outcomes (*55*–*65*). In primary care settings, prevalence of opioid dependence (using DSM-IV criteria) ranged from 3% to 26% (*55*,*56*,*59*). In pain clinic settings, prevalence of addiction ranged from 2% to 14% (*57*,*58*,*60*,*61*,*63*–*65*).

Factors associated with increased risk for misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications (*55*,*62*). Two studies reported on the association between opioid use and risk for overdose (*66*,*67*). One large fair-quality retrospective cohort study found that recent opioid use was associated with increased risk for any overdose events and serious overdose events versus nonuse (*66*). It also found higher doses associated with increased risk. Relative to 1–19 MME/day, the adjusted hazard ratio (HR) for any overdose event (consisting of mostly nonfatal overdose) was 1.44 for 20 to 49 MME/day, 3.73 for 50–99 MME/day, and 8.87 for ≥100 MME/day. A similar pattern was observed for serious overdose. A good-quality population-based, nested case-control study also found a dose-dependent association with risk for overdose death (*67*). Relative to 1–19 MME/day, the adjusted odds ratio (OR) was 1.32 for 20–49 MME/day, 1.92 for 50–99 MME/day, 2.04 for 100–199 MME/day, and 2.88 for ≥200 MME/day.

Findings of increased fracture risk for current opioid use, versus nonuse, were mixed in two studies (*68*,*69*). Two studies found an association between opioid use and increased risk for cardiovascular events (*70*,*71*). Indirect evidence was found for endocrinologic harms (increased use of medications for erectile dysfunction or testosterone from one previously included study; laboratory-defined androgen deficiency from one newly reviewed study) (*72*,*73*). One study found that opioid dosages ≥20 MME/day were associated with increased odds of road trauma among drivers (*74*).

Opioid Dosing Strategies

For KQ3, the body of evidence is rated as type 4 (14 studies contributing; 12 from the original review plus two new studies). For initiation and titration of opioids, the 2014 AHRQ report found insufficient evidence from three fair-quality, open-label trials to determine comparative effectiveness of ER/LA versus immediate-release opioids for titrating patients to stable pain control (*75*,*76*). One new fair-quality cohort study of Veterans Affairs patients found initiation of therapy with an ER/LA opioid associated with greater risk for nonfatal overdose than initiation with an immediate-release opioid, with risk greatest in the first 2 weeks after initiation of treatment (*77*).

For comparative effectiveness and harms of ER/LA opioids, the 2014 AHRQ report included three randomized, head-to-head trials of various ER/LA opioids that found no clear differences in 1-year outcomes related to pain or function (*78–80*) but had methodological shortcomings. A fair-quality retrospective cohort study based on national Veterans Health Administration system pharmacy data found that methadone was associated with lower overall risk for all-cause mortality versus morphine (*81*), and a fair-quality retrospective cohort study based on Oregon Medicaid data found no statistically significant differences between methadone and long-acting morphine in risk for death or overdose symptoms (*82*). However, a new observational study (*83*) found methadone associated with increased risk for overdose versus sustained-release morphine among Tennessee Medicaid patients. The observed inconsistency in study findings suggests that risks of methadone might vary in different settings as a function of different monitoring and management protocols, though more research is needed to understand factors associated with safer methadone prescribing.

For dose escalation, the 2014 AHRQ report included one fair-quality randomized trial that found no differences between more liberal dose escalation and maintenance of current doses after 12 months in pain, function, all-cause withdrawals, or withdrawals due to opioid misuse (*84*). However, the difference in opioid dosages prescribed at the end of the trial was relatively small (mean 52 MME/day with more liberal dosing versus 40 MME/day). Evidence on other comparisons related to opioid dosing strategies (ER/LA versus immediate-release opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled continuous dosing versus as-needed dosing; or opioid rotation versus maintenance of current therapy; long-term effects of strategies for treating acute exacerbations of chronic pain) was not available or too limited to determine effects on long-term clinical outcomes. For example, evidence on the comparative effectiveness of opioid tapering or discontinuation versus maintenance, and of different opioid tapering strategies, was limited to small, poor-quality studies (*85–87*).

Risk Assessment and Mitigation

For KQ4, the body of evidence is rated as type 3 for the accuracy of risk assessment tools and insufficient for the effectiveness of use of risk assessment tools and mitigation strategies in reducing harms (six studies contributing; four from the original review plus two new studies). The 2014 AHRQ report included four studies (*88–91*) on the accuracy of risk assessment instruments, administered prior to opioid therapy initiation, for predicting opioid abuse or misuse. Results for the Opioid Risk Tool (ORT) (*89–91*) were extremely inconsistent; evidence for other risk assessment instruments was very sparse, and studies had serious methodological shortcomings. One additional fair-quality (*92*) and one poor-quality (*93*) study identified for this update compared the predictive accuracy of the ORT, the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), and the Brief Risk Interview. For the ORT, sensitivity was 0.58 and 0.75 and specificity 0.54 and 0.86; for the SOAPP-R, sensitivity was 0.53 and 0.25 and specificity 0.62 and 0.73; and for the Brief Risk Interview, sensitivity was 0.73 and 0.83 and specificity 0.43 and 0.88. For the ORT, positive likelihood ratios ranged from noninformative (positive likelihood ratio close to 1) to moderately useful (positive likelihood ratio >5). The SOAPP-R was associated with noninformative likelihood ratios (estimates close to 1) in both studies.

No study evaluated the effectiveness of risk mitigation strategies (use of risk assessment instruments, opioid management plans, patient education, urine drug testing, use of PDMP data, use of monitoring instruments, more frequent monitoring intervals, pill counts, or use of abuse-deterrent formulations) for improving outcomes related to overdose, addiction, abuse, or misuse.

Effects of Opioid Therapy for Acute Pain on Long-Term Use

For KQ5, the body of evidence is rated as type 3 (two new studies contributing). Two fair-quality retrospective cohort studies found opioid therapy prescribed for acute pain associated with greater likelihood of long-term use. One study evaluated opioid-naïve patients who had undergone low-risk surgery, such as cataract surgery and varicose vein stripping (*94*). Use of opioids within 7 days of surgery was associated with increased risk for use at 1 year. The other study found that among patients with a workers' compensation claim for acute low back pain, compared to patients who did not receive opioids early after injury (defined as use within 15 days following onset of pain), patients who did receive early opioids had an increased likelihood of receiving five or more opioid prescriptions 30–730 days following onset that increased with greater early exposure. Versus no early opioid use, the adjusted OR was 2.08 (95% CI = 1.55–2.78) for 1-140 MME/day and increased to 6.14 (95% confidence interval [CI] = 4.92–7.66) for ≥450 MME/day (*95*).

Summary of the Contextual Evidence Review

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Primary Areas of Focus

Contextual evidence is complementary information that assists in translating the clinical research findings into recommendations. CDC conducted contextual evidence reviews on four topics to supplement the clinical evidence review findings:

- Effectiveness of nonpharmacologic (e.g., cognitive behavioral therapy [CBT], exercise therapy, interventional treatments, and multimodal pain treatment) and nonopioid pharmacologic treatments (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], antidepressants, and anticonvulsants), including studies of any duration.
- Benefits and harms of opioid therapy (including additional studies not included in the clinical evidence review, such as studies that were not restricted to patients with chronic pain, evaluated outcomes at any duration, performed ecological analyses, or used observational study designs other than cohort and case-cohort control studies) related to specific opioids, high-dose therapy, co-prescription with other controlled substances, duration of use, special populations, and potential usefulness of risk stratification/mitigation approaches, in addition to effectiveness of treatments associated with addressing potential harms of opioid therapy (opioid use disorder).
- Clinician and patient values and preferences related to opioids and medication risks, benefits, and use.
- Resource allocation including costs and economic efficiency of opioid therapy and risk mitigation strategies.

CDC also reviewed clinical guidelines that were relevant to opioid prescribing and could inform or complement the CDC recommendations under development (e.g., guidelines on nonpharmacologic and nonopioid pharmacologic treatments and guidelines with recommendations related to specific clinician actions such as urine drug testing or opioid tapering protocols).

Contextual Evidence Review Methods

CDC conducted a contextual evidence review to assist in developing the recommendations by providing an assessment of the balance of benefits and harms, values and preferences, and cost, consistent with the GRADE approach. Given the public health urgency for developing opioid prescribing recommendations, a rapid review was required for the contextual evidence review for the current guideline. Rapid reviews are used when there is a need to streamline the systematic review process to obtain evidence quickly (*96*). Methods used to streamline the process include limiting searches by databases, years, and languages considered, and truncating quality assessment and data abstraction protocols. CDC conducted "rapid reviews" of the contextual evidence on nonpharmacologic and nonopioid pharmacologic treatments, benefits and harms, values and preferences, and resource allocation.

Detailed information about contextual evidence data sources and searches, inclusion criteria, study selection, and data extraction and synthesis are provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/cdc/38027 (http://stacks.cdc.gov/view/cdc/38027)). In brief, CDC conducted systematic literature searches to identify original studies, systematic reviews, and clinical guidelines, depending on the topic being searched. CDC also solicited publication referrals from subject matter experts. Given the need for a rapid review process, grey literature (e.g., literature by academia, organizations, or government in the forms of reports, documents, or proceedings not published by commercial publishers) was not systematically searched. Database sources, including MEDLINE, PsycINFO, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, varied by topic. Multiple reviewers scanned study abstracts identified through the database searches and extracted relevant studies for review. CDC constructed narrative summaries and tables based on relevant articles that met inclusion criteria, which are provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/cdc/38027 (http://stacks.cdc.gov/view/cdc/38027)).

Findings from the contextual reviews provide indirect evidence and should be interpreted accordingly. CDC did not formally rate the quality of evidence for the studies included in the contextual evidence review using the GRADE method. The studies that addressed benefits and harms, values and preferences, and resource allocation most often employed observational methods, used short follow-up periods, and evaluated selected samples. Therefore the strength of the evidence from these contextual review areas was considered to be low, comparable to type 3 or type 4 evidence. The quality of evidence for nonopioid pharmacologic and nonpharmacologic pain treatments was generally rated as moderate, comparable to type 2 evidence, in systematic reviews and clinical guidelines (e.g., for treatment of chronic neuropathic pain, low back pain, osteoarthritis, and fibromyalgia). Similarly, the quality of evidence on pharmacologic and psychosocial opioid use disorder treatment was generally rated as moderate, comparable to type 2 evidence, in systematic reviews and clinical guidelines.

Summary of Findings for Contextual Areas

Full narrative reviews and tables that summarize key findings from the contextual evidence review are provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/cdc/38027 (http://stacks.cdc.gov/view/cdc/38027)).

Effectiveness of Nonpharmacologic and Nonopioid Pharmacologic Treatments

Several nonpharmacologic and nonopioid pharmacologic treatments have been shown to be effective in managing chronic pain in studies ranging in duration from 2 weeks to 6 months. For example, CBT that trains patients in behavioral techniques and helps patients modify situational factors and cognitive processes that exacerbate pain has small positive effects on disability and catastrophic thinking (*97*). Exercise therapy can help reduce pain and improve function in chronic low back pain (*98*), improve function and reduce pain in osteoarthritis of the knee (*99*) and hip (*100*), and improve well-being, fibromyalgia symptoms, and physical function in fibromyalgia (*101*). Multimodal and multidisciplinary therapies (e.g., therapies that combine exercise and related therapies with psychologically based approaches) can help reduce pain and improve function more effectively than single modalities (*102*,*103*). Nonopioid pharmacologic approaches used for pain include analgesics such as acetaminophen, NSAIDs, and cyclooxygenase 2 (COX-2) inhibitors; selected anticonvulsants; and selected antidepressants (particularly tricyclics and serotonin and norepinephrine reuptake inhibitors [SNRIs]). Multiple guidelines recommend acetaminophen as first-line pharmacotherapy for osteoarthritis (*104*–*109*) or for low back pain (*110*) but note that it should be avoided in liver failure and that dosage should be reduced in patients with hepatic insufficiency or a history of alcohol abuse (*109*). Although guidelines also recommend NSAIDs as first-line treatment for osteoarthritis or low back pain (*106*,*110*), NSAIDs and COX-2 inhibitors do have risks, including gastrointestinal bleeding or perforation as well as renal and cardiovascular risks (*111*). FDA has recently strengthened existing label warnings that NSAIDs increase risks for heart attack and stroke, including that these risks might increase with longer use or at higher doses (*112*). Several guidelines agree that first- and second-line drugs for neuropathic pain include anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, and SNRIs (*113*–*116*). Interventional approaches such as epidural injection for certain conditions (e.g., lumbar radiculopathy) can provide short-term improvement in pain (*117*–*119*). Epidural injection has been associated with rare but serious adverse events, including loss of vision, stroke, paralysis, and death (*120*).

Benefits and Harms of Opioid Therapy

Balance between benefits and harms is a critical factor influencing the strength of clinical recommendations. In particular, CDC considered what is known from the epidemiology research about benefits and harms related to specific opioids and formulations, high dose therapy, co-prescription with other controlled substances, duration of use, special populations, and risk stratification and mitigation approaches. Additional information on benefits and harms of long-term opioid therapy from studies meeting rigorous selection criteria is provided in the clinical evidence review (e.g., see KQ2). CDC also considered the number of persons experiencing chronic pain, numbers potentially benefiting from opioids, and numbers affected by opioid-related harms. A review of these data is presented in the background section of this document, with detailed information provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/cdc/38027 (http://stacks.cdc.gov/view/cdc/38027)). Finally, CDC considered the effectiveness of treatments that addressed potential harms of opioid therapy (opioid use disorder).

Regarding specific opioids and formulations, as noted by FDA, there are serious risks of ER/LA opioids, and the indication for this class of medications is for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment in patients for whom other 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

(*121*). Time-scheduled opioid use was associated with substantially higher average daily opioid dosage than as-needed opioid use in one study (*122*). Methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for pain. Methadone has been found to account for as much as a third of opioid-related overdose deaths involving single or multiple drugs in states that participated in the Drug Abuse Warning Network, which was more than any opioid other than oxycodone, despite representing <2% of opioid prescriptions outside of opioid treatment programs in the United States; further, methadone was involved in twice as many single-drug deaths as any other prescription opioid (*123*).

Regarding high-dose therapy, several epidemiologic studies that were excluded from the clinical evidence review because patient samples were not restricted to patients with chronic pain also examined the association between opioid dosage and overdose risk (*23*,*24*,*124*–*126*). Consistent with the clinical evidence review, the contextual review found that opioid-related overdose risk is dose-dependent, with higher opioid dosages associated with increased overdose risk. Two of these studies (*23*,*24*), as well as the two studies in the clinical evidence review (*66*,*67*), evaluated similar MME/day dose ranges for association with overdose risk. In these four studies, compared with opioids prescribed at <20 MME/day, the odds of overdose among patients prescribed opioids for chronic nonmalignant pain were between 1.3 (*67*) and 1.9 (*24*) for dosages of 20 to <50 MME/day, between 1.9 (*67*) and 4.6 (*24*) for dosages of 50 to <100 MME/day, and between 2.0 (*67*) and 8.9 (*66*) for dosages of ≥100 MME/day. Compared with dosages of 1-<20 MME/day, absolute risk difference approximation for 50-<100 MME/day was 0.15% for fatal overdose (*24*) and 1.40% for any overdose (*66*), and for ≥100 MME/day was 0.25% for fatal overdose (*24*) and 4.04% for any overdose (*66*). A recent study of Veterans Health Administration patients with chronic pain found that patients who died of overdoses related to opioids were prescribed higher opioid dosages (mean: 98 MME/day; median: 60 MME/day) than controls (mean: 48 MME/day, median: 25 MME/day) (*127*). Finally, another recent study of overdose deaths among state residents with and without opioid prescriptions revealed that prescription opioid-related overdose mortality rates rose rapidly up to prescribed doses of 200 MME/day, after which the mortality rates continued to increase but grew more gradually (*128*). A listing of common opioid medications and their MME equivalents is provided (Table 2).

Regarding coprescription of opioids with benzodiazepines, epidemiologic studies suggest that concurrent use of benzodiazepines and opioids might put patients at greater risk for potentially fatal overdose. Three studies of fatal overdose deaths found evidence of concurrent benzodiazepine use in 31%–61% of decedents (*67*,*128*,*129*). In one of these studies (*67*), among decedents who received an opioid prescription, those whose deaths were related to opioids were more likely to have obtained opioids from multiple physicians and pharmacies than decedents whose deaths were not related to opioids.

Regarding duration of use, patients can experience tolerance and loss of effectiveness of opioids over time (*130*). Patients who do not experience clinically meaningful pain relief early in treatment (i.e., within 1 month) are unlikely to experience pain relief with longer-term use (*131*).

Regarding populations potentially at greater risk for harm, risk is greater for patients with sleep apnea or other causes of sleep-disordered breathing, patients with renal or hepatic insufficiency, older adults, pregnant women, patients with depression or other mental health conditions, and patients with alcohol or other substance use disorders. Interpretation of clinical data on the effects of opioids on sleep-disordered breathing is difficult because of the types of study designs and methods employed, and there is no clear consensus regarding association with risk for developing obstructive sleep apnea syndrome (*132*). However, opioid therapy can decrease respiratory drive, a high percentage of patients on long-term opioid therapy have been reported to have an abnormal apnea-hypopnea index (*133*), opioid therapy can worsen central sleep apnea in obstructive sleep apnea patients, and it can cause further desaturation in obstructive sleep apnea patients not on continuous positive airway pressure (CPAP) (*31*). Reduced renal or hepatic function can result in greater peak effect and longer duration of action and reduce the dose at which respiratory depression and overdose occurs (*134*). Age-related changes in patients aged ≥65 years, such as reduced renal function and medication clearance, even in the absence of renal disease (*135*), result in a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose. Older adults might also be at increased risk for falls and fractures related to opioids (*136*–*138*). Opioids used in pregnancy can be associated with additional risks to both mother and fetus. Some studies have shown an association of opioid use in pregnancy with birth defects, including neural tube defects (*139*,*140*), congenital heart defects (*140*), and gastroschisis (*140*); preterm delivery (*141*), poor fetal growth (*141*), and stillbirth (*141*). Importantly, in some cases, opioid use during pregnancy leads to neonatal opioid withdrawal syndrome (*142*). Patients with mental health comorbidities and patients with histories of substance use disorders might be at higher risk than other patients for opioid use disorder (*62*,*143*,*144*). Recent analyses found that depressed patients were at higher risk for drug overdose than patients without depression, particularly at higher opioid dosages, although investigators were unable to distinguish unintentional overdose from suicide attempts (*145*). In case-control and case-cohort studies, substance abuse/dependence was more prevalent among patients experiencing overdose than among patients not experiencing overdose (12% versus 6% [*66*], 40% versus 10% [*24*], and 26% versus 9% [*23*]).

Regarding risk stratification approaches, limited evidence was found regarding benefits and harms. Potential benefits of PDMPs and urine drug testing include the ability to identify patients who might be at higher risk for opioid overdose or opioid use disorder, and help determine which patients will benefit from greater caution and increased monitoring or interventions when risk factors are present. For example, one study found that most fatal overdoses could be identified retrospectively on the basis of two pieces of information, multiple prescribers and high total daily opioid dosage, both important risk factors for overdose (*124*,*146*) that are available to prescribers in the PDMP (*124*). However, limited evaluation of PDMPs at the state level has revealed mixed effects on changes in prescribing and mortality outcomes (*28*). Potential harms of risk stratification include underestimation of risks of opioid therapy when screening tools are not adequately sensitive, as well as potential overestimation of risk, which could lead to inappropriate clinical decisions.

Regarding risk mitigation approaches, limited evidence was found regarding benefits and harms. Although no studies were found to examine prescribing of naloxone with opioid pain medication in primary care settings, naloxone distribution through community-based programs providing prevention services for substance users has been demonstrated to be associated with decreased risk for opioid overdose death at the community level (*147*).

Concerns have been raised that prescribing changes such as dose reduction might be associated with unintended negative consequences, such as patients seeking heroin or other illicitly obtained opioids (*148*) or interference with appropriate pain treatment (*149*). With the exception of a study noting an association between an abuse-deterrent formulation of OxyContin and heroin use, showing that some patients in qualitative interviews reported switching to another opioid, including heroin, for many reasons, including cost and availability as well as ease of use (*150*), CDC did not identify studies evaluating these potential outcomes.

Finally, regarding the effectiveness of opioid use disorder treatments, methadone and buprenorphine for opioid use disorder have been found to increase retention in treatment and to decrease illicit opioid use among patients with opioid use disorder involving heroin (*151–153*). Although findings are mixed, some studies suggest that effectiveness is enhanced when psychosocial treatments (e.g., contingency management, community reinforcement, psychotherapeutic counseling, and family therapy) are used in conjunction with medication-assisted therapy; for example, by reducing opioid misuse and increasing retention during maintenance therapy, and improving compliance after detoxification (*154,155*).

Clinician and Patient Values and Preferences

Clinician and patient values and preferences can inform how benefits and harms of long-term opioid therapy are weighted and estimate the effort and resources required to effectively provide implementation support. Many physicians lack confidence in their ability to prescribe opioids safely (*156*), to predict (*157*) or detect (*158*) prescription drug abuse, and to discuss abuse with their patients (*158*). Although clinicians have reported favorable beliefs and attitudes about improvements in pain and quality of life attributed to opioids (*159*), most consider prescription drug abuse to be a "moderate" or "big" problem in their community, and large proportions are "very" concerned about opioid addiction (55%) and death (48%) (*160*). Clinicians do not consistently use practices intended to decrease the risk for misuse, such as PDMPs (*161,162*), urine drug testing (*163*), and opioid treatment agreements (*164*). This is likely due in part to challenges related to registering for PDMP access and logging into the PDMP (which can interrupt normal clinical workflow if data are not integrated into electronic health record systems) (*165*), competing clinical demands, perceived inadequate time to discuss the rationale for urine drug testing and to order confirmatory testing, and feeling unprepared to interpret and address results (*166*).

Many patients do not have an opinion about "opioids" or know what this term means (*167*). Most are familiar with the term "narcotics." About a third associated "narcotics" with addiction or abuse, and about half feared "addiction" from long-term "narcotic" use (*168*). Most patients taking opioids experience side effects (73% of patients taking hydrocodone for noncancer pain [*11*], 96% of patients taking opioids for chronic pain [*12*]), and side effects, rather than pain relief, have been found to explain most of the variation in patients' preferences related to taking opioids (*12*). For example, patients taking hydrocodone for noncancer pain commonly reported side effects including dizziness, headache, fatigue, drowsiness, nausea, vomiting, and constipation (*11*). Patients with chronic pain in focus groups emphasized effectiveness of goal setting for increasing motivation and functioning (*168*). Patients taking high dosages report reliance on opioids despite ambivalence about their benefits (*169*) and regardless of pain reduction, reported problems, concerns, side effects, or perceived helpfulness (*13*).

Resource Allocation

Resource allocation (cost) is an important consideration in understanding the feasibility of clinical recommendations. CDC searched for evidence on opioid therapy compared with other treatments; costs of misuse, abuse, and overdose from prescription opioids; and costs of specific risk mitigation strategies (e.g., urine drug testing). Yearly direct and indirect costs related to prescription opioids have been estimated (based on studies published since 2010) to be $53.4 billion for nonmedical use of prescription opioids (*170*); $55.7 billion for abuse, dependence (i.e., opioid use disorder), and misuse of prescription opioids (*171*), and $20.4 billion for direct and indirect costs related to opioid-related overdose alone (*172*). In 2012, total expenses for outpatient prescription opioids were estimated at $9.0 billion, an increase of 120% from 2002 (*173*). Although there are perceptions that opioid therapy for chronic pain is less expensive than more time-intensive nonpharmacologic management approaches, many pain treatments, including acetaminophen, NSAIDs, tricyclic antidepressants, and massage therapy, are associated with lower mean and median annual costs compared with opioid therapy (*174*). COX-2 inhibitors, SNRIs, anticonvulsants, topical analgesics, physical therapy, and CBT are also associated with lower median annual costs compared with opioid therapy (*174*). Limited information was found on costs of strategies to decrease risks associated with opioid therapy; however, urine drug testing, including screening and confirmatory tests, has been estimated to cost $211–$363 per test (*175*).

Recommendations

Top

The recommendations are grouped into three areas for consideration:

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

There are 12 recommendations (Box 1). Each recommendation is followed by a rationale for the recommendation, with considerations for implementation noted. In accordance with the ACIP GRADE process, CDC based the recommendations on consideration of the clinical evidence, contextual evidence (including benefits and harms, values and preferences, resource allocation), and expert opinion. For each recommendation statement, CDC notes the recommendation category (A or B) and the type of the evidence (1, 2, 3, or 4) supporting the statement (Box 2). Expert opinion is reflected within each of the recommendation rationales. While there was not an attempt to reach consensus among experts, experts from the Core Expert Group and from the Opioid Guideline Workgroup ("experts") expressed overall, general support for all recommendations. Where differences in expert opinion emerged for detailed actions within the clinical recommendations or for implementation considerations, CDC notes the differences of opinion in the supporting rationale statements.

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 (*47*) and GRADE process (*48*), category A recommendations were made, even with type 3 and 4 evidence, when there was broad agreement that the advantages of a clinical action greatly outweighed the disadvantages based on a consideration of benefits and harms, values and preferences, and resource allocation. Category B recommendations were made when there was broad agreement that the advantages and disadvantages of a clinical action were more balanced, but advantages were significant enough to warrant a recommendation. All recommendations are category A recommendations, with the exception of recommendation 10, which is rated as category B. Recommendations were associated with a range of evidence types, from type 2 to type 4.

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

- No evidence shows a long-term benefit of opioids in pain and function versus no opioids for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized trials ≤6 weeks in duration).
- Extensive evidence shows the possible harms of opioids (including opioid use disorder, overdose, and motor vehicle injury).
- Extensive evidence suggests some benefits of nonpharmacologic and nonopioid pharmacologic treatments compared with long-term opioid therapy, with less harm.

Determining When to Initiate or Continue Opioids for Chronic Pain

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

Patients with pain should receive treatment that provides the greatest benefits relative to risks. The contextual evidence review found that many nonpharmacologic therapies, including physical therapy, weight loss for knee osteoarthritis, psychological therapies such as CBT, and certain interventional procedures can ameliorate chronic pain. There is high-quality evidence that exercise therapy (a prominent modality in physical therapy) for hip (*100*) or knee (*99*) osteoarthritis reduces pain and improves function immediately after treatment and that the improvements are sustained for at least 2–6 months. Previous guidelines have strongly recommended aerobic, aquatic, and/or resistance exercises for patients with osteoarthritis of the knee or hip (*176*). Exercise therapy also can help reduce pain and improve function in low back pain and can improve global well-being and physical function in fibromyalgia (*98*,*101*). Multimodal therapies and multidisciplinary biopsychosocial rehabilitation-combining approaches (e.g., psychological therapies with exercise) can reduce long-term pain and disability compared with usual care and compared with physical treatments (e.g., exercise) alone. Multimodal therapies are not always available or reimbursed by insurance and can be time-consuming and costly for patients. Interventional approaches such as arthrocentesis and intraarticular glucocorticoid injection for pain associated with rheumatoid arthritis (*117*) or osteoarthritis (*118*) and subacromial corticosteroid injection for rotator cuff disease (*119*) can provide short-term improvement in pain and function. Evidence is insufficient to determine the extent to which repeated glucocorticoid injection increases potential risks such as articular cartilage changes (in osteoarthritis) and sepsis (*118*). Serious adverse events are rare but have been reported with epidural injection (*120*).

Several nonopioid pharmacologic therapies (including acetaminophen, NSAIDs, and selected antidepressants and anticonvulsants) are effective for chronic pain. In particular, acetaminophen and NSAIDs can be useful for arthritis and low back pain. Selected anticonvulsants such as pregabalin and gabapentin can improve pain in diabetic neuropathy and post-herpetic neuralgia (contextual evidence review). Pregabalin, gabapentin, and carbamazepine are FDA-approved for treatment of certain neuropathic pain conditions, and pregabalin is FDA approved for fibromyalgia management. In patients with or without depression, tricyclic antidepressants and SNRIs provide effective analgesia for neuropathic pain conditions including diabetic neuropathy and post-herpetic neuralgia, often at lower dosages and with a shorter time to onset of effect than for treatment of depression (see contextual evidence review). Tricyclics and SNRIs can also relieve fibromyalgia symptoms. The SNRI duloxetine is FDA-approved for the treatment of diabetic neuropathy and fibromyalgia. Because patients with chronic pain often suffer from concurrent depression (*144*), and depression can exacerbate physical symptoms including pain (*177*), patients with co-occurring pain and depression are especially likely to benefit from antidepressant medication (see Recommendation 8). Nonopioid pharmacologic therapies are not generally associated with substance use disorder, and the numbers of fatal overdoses associated with nonopioid medications are a fraction of those associated with opioid medications (contextual evidence review). For example, acetaminophen, NSAIDs, and opioid pain medication were involved in 881, 228, and 16,651 pharmaceutical overdose deaths in the United States in 2010 (*178*). However, nonopioid pharmacologic therapies are associated with certain risks, particularly in older patients, pregnant patients, and patients with certain co-morbidities such as cardiovascular, renal, gastrointestinal, and liver disease (see contextual evidence review). For example, acetaminophen can be hepatotoxic at dosages of > 3-4 grams/day and at lower dosages in patients with chronic alcohol use or liver disease (*109*). NSAID use has been associated with gastritis, peptic ulcer disease, cardiovascular events (*111*,*112*), and fluid retention, and most NSAIDs (choline magnesium trilisate and selective COX-2 inhibitors are exceptions) interfere with platelet aggregation (*179*). Clinicians should review FDA-approved labeling including boxed warnings before initiating treatment with any pharmacologic therapy.

Although opioids can reduce pain during short-term use, the clinical evidence review found insufficient evidence to determine whether pain relief is sustained and whether function or quality of life improves with long-term opioid therapy (KQ1). While benefits for pain relief, function, and quality of life with long-term opioid use for chronic pain are uncertain, risks associated with long-term opioid use are clearer and significant. Based on the clinical evidence review, long-term opioid use for chronic pain is associated with serious risks including increased risk for opioid use disorder, overdose, myocardial infarction, and motor vehicle injury (KQ2). At a population level, more than 165,000 persons in the United States have died from opioid pain-medication-related overdoses since 1999 (see Contextual Evidence Review).

Integrated pain management requires coordination of medical, psychological, and social aspects of health care and includes primary care, mental health care, and specialist services when needed (*180*). Nonpharmacologic physical and psychological treatments such as exercise and CBT are approaches that encourage active patient participation in the care plan, address the effects of pain in the patient's life, and can result in sustained improvements in pain and function without apparent risks. Despite this, these therapies are not always or fully covered by insurance, and access and cost can be barriers for patients. For many patients, aspects of these approaches can be used even when there is limited access to specialty care. For example, previous guidelines have strongly recommended aerobic, aquatic, and/or resistance exercises for patients with osteoarthritis of the knee or hip (*176*) and maintenance of activity for patients with low back pain (*110*). A randomized trial found no difference in reduced chronic low back pain intensity, frequency or disability between patients assigned to relatively low-cost group aerobics and individual physiotherapy or muscle reconditioning sessions (*181*). Low-cost options to integrate exercise include brisk walking in public spaces or use of public recreation facilities for group exercise. CBT addresses psychosocial contributors to pain and improves function (*97*). Primary care clinicians can integrate elements of a cognitive behavioral approach into their practice by encouraging patients to take an active role in the care plan, by supporting patients in engaging in beneficial but potentially anxiety-provoking activities, such as exercise (*179*), or by providing

education in relaxation techniques and coping strategies. In many locations, there are free or low-cost patient support, self-help, and educational community-based programs that can provide stress reduction and other mental health benefits. Patients with more entrenched anxiety or fear related to pain, or other significant psychological distress, can be referred for formal therapy with a mental health specialist (e.g., psychologist, psychiatrist, clinical social worker). Multimodal therapies should be considered for patients not responding to single-modality therapy, and combinations should be tailored depending on patient needs, cost, and convenience.

To guide patient-specific selection of therapy, clinicians should evaluate patients and establish or confirm the diagnosis. Detailed recommendations on diagnosis are provided in other guidelines (*110*,*179*), but evaluation should generally include a focused history, including history and characteristics of pain and potentially contributing factors (e.g., function, psychosocial stressors, sleep) and physical exam, with imaging or other diagnostic testing only if indicated (e.g., if severe or progressive neurologic deficits are present or if serious underlying conditions are suspected) (*110*,*179*). For complex pain syndromes, pain specialty consultation can be considered to assist with diagnosis as well as management. Diagnosis can help identify disease-specific interventions to reverse or ameliorate pain; for example, improving glucose control to prevent progression of diabetic neuropathy; immune-modulating agents for rheumatoid arthritis; physical or occupational therapy to address posture, muscle weakness, or repetitive occupational motions that contribute to musculoskeletal pain; or surgical intervention to relieve mechanical/compressive pain (*179*). The underlying mechanism for most pain syndromes can be categorized as neuropathic (e.g., diabetic neuropathy, postherpetic neuralgia, fibromyalgia), or nociceptive (e.g., osteoarthritis, muscular back pain). The diagnosis and pathophysiologic mechanism of pain have implications for symptomatic pain treatment with medication. For example, evidence is limited or insufficient for improved pain or function with long-term use of opioids for several chronic pain conditions for which opioids are commonly prescribed, such as low back pain (*182*), headache (*183*), and fibromyalgia (*184*). Although NSAIDs can be used for exacerbations of nociceptive pain, other medications (e.g., tricyclics, selected anticonvulsants, or transdermal lidocaine) generally are recommended for neuropathic pain. In addition, improvement of neuropathic pain can begin weeks or longer after symptomatic treatment is initiated (*179*). Medications should be used only after assessment and determination that expected benefits outweigh risks given patient-specific factors. For example, clinicians should consider falls risk when selecting and dosing potentially sedating medications such as tricyclics, anticonvulsants, or opioids, and should weigh risks and benefits of use, dose, and duration of NSAIDs when treating older adults as well as patients with hypertension, renal insufficiency, or heart failure, or those with risk for peptic ulcer disease or cardiovascular disease. Some guidelines recommend topical NSAIDs for localized osteoarthritis (e.g., knee osteoarthritis) over oral NSAIDs in patients aged ≥ 75 years to minimize systemic effects (*176*).

Experts agreed that opioids should not be considered first-line or routine therapy for chronic pain (i.e., pain continuing or expected to continue >3 months or past the time of normal tissue healing) outside of active cancer, palliative, and end-of-life care, given small to moderate short-term benefits, uncertain long-term benefits, and potential for serious harms; although evidence on long-term benefits of nonopioid therapies is also limited, these therapies are also associated with short-term benefits, and risks are much lower. This does not mean that patients should be required to sequentially "fail" nonpharmacologic and nonopioid pharmacologic therapy before proceeding to opioid therapy. Rather, expected benefits specific to the clinical context should be weighed against risks before initiating therapy. In some clinical contexts (e.g., headache or fibromyalgia), expected benefits of initiating opioids are unlikely to outweigh risks regardless of previous nonpharmacologic and nonopioid pharmacologic therapies used. In other situations (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 addition, when opioid pain medication is used, it is more likely to be effective if integrated with nonpharmacologic therapy. Nonpharmacologic approaches such as exercise and CBT should be used to reduce pain and improve function in patients with chronic pain. Nonopioid pharmacologic therapy should be used when benefits outweigh risks and should be combined with nonpharmacologic therapy to reduce pain and improve function. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate, to provide greater benefits to patients in improving pain and function.

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

The clinical evidence review 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. In addition, studies on currently available risk assessment instruments were sparse and showed inconsistent results (KQ4). The clinical evidence review for the current guideline considered studies with outcomes examined at ≥1 year that compared opioid use versus nonuse or placebo. Studies of opioid therapy for chronic pain that did not have a nonopioid control group have found that although many patients discontinue opioid therapy for chronic noncancer pain due to adverse effects or insufficient pain relief, there is weak evidence that patients who are able to continue opioid therapy for at least 6 months can experience clinically significant pain relief and insufficient evidence that function or quality of life improves (*185*). These findings suggest that it is very difficult for clinicians to predict whether benefits of opioids for chronic pain will outweigh risks of ongoing treatment for individual patients. Opioid therapy should not be initiated without consideration of an "exit strategy" to be used if the therapy is unsuccessful.

Experts agreed that before opioid therapy is initiated for chronic pain outside of active cancer, palliative, and end-of-life care, clinicians should determine how effectiveness will be evaluated and should establish treatment goals with patients. Because the line between acute pain and initial chronic pain is not always clear, it might be difficult for clinicians to determine when they are initiating opioids for chronic pain rather than treating acute pain. Pain lasting longer than 3 months or past the time of normal tissue healing (which could be substantially shorter than 3 months, depending on the condition) is generally no longer considered acute. However, establishing treatment goals with a patient who has already received opioid therapy for 3 months would defer this discussion well past the point of initiation of opioid therapy for chronic pain. Clinicians often write prescriptions for long-term use in 30-day increments, and opioid prescriptions written for ≥30 days are likely to represent initiation or continuation of long-term opioid therapy. Before writing an opioid prescription for ≥30 days, clinicians should establish treatment goals with patients. Clinicians seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy. Although the clinical evidence review did not find studies evaluating the effectiveness of written agreements or treatment plans

(KQ4), clinicians and patients who set a plan in advance will clarify expectations regarding how opioids will be prescribed and monitored, as well as situations in which opioids will be discontinued or doses tapered (e.g., if treatment goals are not met, opioids are no longer needed, or adverse events put the patient at risk) to improve patient safety.

Experts thought that goals should include improvement in both pain relief and function (and therefore in quality of life). However, there are some clinical circumstances under which reductions in pain without improvement in physical function might be a more realistic goal (e.g., diseases typically associated with progressive functional impairment or catastrophic injuries such as spinal cord trauma). Experts noted that function can include emotional and social as well as physical dimensions. In addition, experts emphasized that mood has important interactions with pain and function. Experts agreed that clinicians may use validated instruments such as the three-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale (*186*) to track patient outcomes. Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function (*187*). Monitoring progress toward patient-centered functional goals (e.g., walking the dog or walking around the block, returning to part-time work, attending family sports or recreational activities) can also contribute to the assessment of functional improvement. Clinicians should use these goals in assessing benefits of opioid therapy for individual patients and in weighing benefits against risks of continued opioid therapy (see Recommendation 7, including recommended intervals for follow-up). Because depression, anxiety, and other psychological co-morbidities often coexist with and can interfere with resolution of pain, clinicians should use validated instruments to assess for these conditions (see Recommendation 8) and ensure that treatment for these conditions is optimized. If patients receiving opioid therapy for chronic pain do not experience meaningful improvements in both pain and function compared with prior to initiation of opioid therapy, clinicians should consider working with patients to taper and discontinue opioids (see Recommendation 7) and should use nonpharmacologic and nonopioid pharmacologic approaches to pain management (see Recommendation 1).

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

The clinical evidence review did not find studies evaluating effectiveness of patient education or opioid treatment plans as risk-mitigation strategies (KQ4). However, the contextual evidence review found that many patients lack information about opioids and identified concerns that some clinicians miss opportunities to effectively communicate about safety. Given the substantial evidence gaps on opioids, uncertain benefits of long-term use, and potential for serious harms, patient education and discussion before starting opioid therapy are critical so that patient preferences and values can be understood and used to inform clinical decisions. Experts agreed that essential elements to communicate to patients before starting and periodically during opioid therapy include realistic expected benefits, common and serious harms, and expectations for clinician and patient responsibilities to mitigate risks of opioid therapy.

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

- Be explicit and realistic about expected benefits of opioids, explaining that while opioids can reduce pain during short-term use, there is no good evidence that opioids improve pain or function with long-term use, and that complete relief of pain is unlikely (clinical evidence review, KQ1).
- Emphasize improvement in function as a primary goal and that function can improve even when pain is still present.
- Advise patients about serious adverse effects of opioids, including potentially fatal respiratory depression and development of a potentially serious lifelong opioid use disorder that can cause distress and inability to fulfill major role obligations.
- 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. Stool softeners or laxatives might be needed.
- Discuss effects that opioids might have on ability to safely operate a vehicle, particularly when opioids are initiated, when dosages are increased, or when other central nervous system depressants, such as benzodiazepines or alcohol, are used concurrently.
- Discuss increased risks for opioid use disorder, respiratory depression, and death at higher dosages, along with the importance of taking only the amount of opioids prescribed, i.e., not taking more opioids or taking them more often.
- Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, illicit drugs such as heroin, or other opioids.
- Discuss risks to household members and other individuals if opioids are intentionally or unintentionally shared with others for whom they are not prescribed, including the possibility that others might experience overdose at the same or at lower dosage than prescribed for the patient, and that young children are susceptible to unintentional ingestion. Discuss storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids (*188*).
- Discuss the importance of periodic reassessment to ensure that opioids are helping to meet patient goals and to allow opportunities for opioid discontinuation and consideration of additional nonpharmacologic or nonopioid pharmacologic treatment options if opioids are not effective or are harmful.
- Discuss planned use of precautions to reduce risks, including use of prescription drug monitoring program information (see Recommendation 9) and urine drug testing (see Recommendation 10). Consider including discussion of naloxone use for overdose reversal (see Recommendation 8).
- Consider whether cognitive limitations might interfere with management of opioid therapy (for older adults in particular) and, if so, determine whether a caregiver can responsibly co-manage medication therapy. Discuss the importance of reassessing safer medication use with both the patient and caregiver.

Given the possibility that benefits of opioid therapy might diminish or that risks might become more prominent over time, it is important that clinicians review expected benefits and risks of continued opioid therapy with patients periodically, at least every 3 months (see Recommendation 7).

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

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting

(ER/LA) opioids (recommendation category: A, evidence type: 4).

ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of opioids such as oxycodone, oxymorphone, hydrocodone, and morphine. The clinical evidence review found a fair-quality study showing a higher risk for overdose among patients initiating treatment with ER/LA opioids than among those initiating treatment with immediate-release opioids (*77*). The clinical evidence review did not find evidence that continuous, time-scheduled use of ER/LA opioids is more effective or safer than intermittent use of immediate-release opioids or that time-scheduled use of ER/LA opioids reduces risks for opioid misuse or addiction (KQ3).

In 2014, the FDA modified the labeling for ER/LA opioid pain medications, noting serious risks and recommending that ER/LA opioids be reserved for "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment" when "alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain" and not used as "as needed" pain relievers (*121*). FDA has also noted that some ER/LA opioids are only appropriate for opioid-tolerant patients, defined as patients who have received certain dosages of opioids (e.g., 60 mg daily of oral morphine, 30 mg daily of oral oxycodone, or equianalgesic dosages of other opioids) for at least 1 week (*189*). Time-scheduled opioid use can be associated with greater total average daily opioid dosage compared with intermittent, as-needed opioid use (contextual evidence review). In addition, experts indicated that there was not enough evidence to determine the safety of using immediate-release opioids for breakthrough pain when ER/LA opioids are used for chronic pain outside of active cancer pain, palliative care, or end-of-life care, and that this practice might be associated with dose escalation.

Abuse-deterrent technologies have been employed to prevent manipulation intended to defeat extended-release properties of ER/LA opioids and to prevent opioid use by unintended routes of administration, such as injection of oral opioids. As indicated in FDA guidance for industry on evaluation and labeling of abuse-deterrent opioids (*190*), although abuse-deterrent technologies are expected to make manipulation of opioids more difficult or less rewarding, they do not prevent opioid abuse through oral intake, the most common route of opioid abuse, and can still be abused by nonoral routes. The "abuse-deterrent" label does not indicate that there is no risk for abuse. No studies were found in the clinical evidence review assessing the effectiveness of abuse-deterrent technologies as a risk mitigation strategy for deterring or preventing abuse. In addition, abuse-deterrent technologies do not prevent unintentional overdose through oral intake. Experts agreed that recommendations could not be offered at this time related to use of abuse-deterrent formulations.

In comparing different ER/LA formulations, the clinical evidence review found inconsistent results for overdose risk with methadone versus other ER/LA opioids used for chronic pain (KQ3). The contextual evidence review found that methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for chronic pain. In addition, methadone is associated with cardiac arrhythmias along with QT prolongation on the electrocardiogram, and it has complicated pharmacokinetics and pharmacodynamics, including a long and variable half-life and peak respiratory depressant effect occurring later and lasting longer than peak analgesic effect. Experts noted that the pharmacodynamics of methadone are subject to more inter-individual variability than other opioids. In regard to other ER/LA opioid formulations, experts noted that the absorption and pharmacodynamics of transdermal fentanyl are complex, with gradually increasing serum concentration during the first part of the 72-hour dosing interval, as well as variable absorption based on factors such as external heat. In addition, the dosing of transdermal fentanyl in mcg/hour, which is not typical for a drug used by outpatients, can be confusing. Experts thought that these complexities might increase the risk for fatal overdose when methadone or transdermal fentanyl is prescribed to a patient who has not used it previously or by clinicians who are not familiar with its effects.

Experts agreed that for patients not already receiving opioids, clinicians should not initiate opioid treatment with ER/LA opioids and should not prescribe ER/LA opioids for intermittent use. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received 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 drugs among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations. Although there might be situations in which clinicians need to prescribe immediate-release and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to immediate-release opioids by temporarily using lower dosages of both), in general, avoiding the use of immediate-release opioids in combination with ER/LA opioids is preferable, given potentially increased risk and diminishing returns of such an approach for chronic pain.

When an ER/LA opioid is prescribed, using one with predictable pharmacokinetics and pharmacodynamics is preferred to minimize unintentional overdose risk. In particular, unusual characteristics of methadone and of transdermal fentanyl make safe prescribing of these medications for pain especially challenging.

- 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 that contains further guidance regarding methadone prescribing for pain has been published previously (*191*).
- Because dosing effects of transdermal fentanyl are often misunderstood by both clinicians and patients, only clinicians who are familiar with the dosing and absorption properties of transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.

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

Benefits of high-dose opioids for chronic pain are not established. The clinical evidence review found only one study (*84*) addressing effectiveness of dose titration for outcomes related to pain control, function, and quality of life (KQ3). This randomized trial found no difference in pain or function between a more liberal opioid dose escalation strategy and maintenance of current dosage. (These groups were prescribed average dosages of 52 and 40 MME/day.

respectively, at the end of the trial.) At the same time, risks for serious harms related to opioid therapy increase at higher opioid dosage. The clinical evidence review found that higher opioid dosages are associated with increased risks for motor vehicle injury, opioid use disorder, and overdose (KQ2). The clinical and contextual evidence reviews found that opioid overdose risk increases in a dose-response manner, that dosages of 50–<100 MME/day have been found to increase risks for opioid overdose by factors of 1 9 to 4.6 compared with dosages of 1–<20 MME/day, and that dosages ≥100 MME/day are associated with increased risks of overdose 2.0–8.9 times the risk at 1–<20 MME/day. In a national sample of Veterans Health Administration patients with chronic pain who were prescribed opioids, mean prescribed opioid dosage among patients who died from opioid overdose was 98 MME (median 60 MME) compared with mean prescribed opioid dosage of 48 MME (median 25 MME) among patients not experiencing fatal overdose (*127*).

The contextual evidence review found that although there is not a single dosage threshold below which overdose risk is eliminated, holding dosages <50 MME/day would likely reduce risk among a large proportion of patients who would experience fatal overdose at higher prescribed dosages. Experts agreed that lower dosages of opioids reduce the risk for overdose, but that a single dosage threshold for safe opioid use could not be identified. Experts noted that daily opioid dosages close to or greater than 100 MME/day are associated with significant risks, that dosages <50 MME/day are safer than dosages of 50–100 MME/day, and that dosages <20 MME/day are safer than dosages of 20–50 MME/day. One expert thought that a specific dosage at which the benefit/risk ratio of opioid therapy decreases could not be identified. Most experts agreed that, in general, increasing dosages to 50 or more MME/day increases overdose risk without necessarily adding benefits for pain control or function and that clinicians should carefully reassess evidence of individual benefits and risks when considering increasing opioid dosages to ≥50 MME/day. Most experts also agreed that opioid dosages should not be increased to ≥90 MME/day without careful justification based on diagnosis and on individualized assessment of benefits and risks.

When opioids are used for chronic pain outside of active cancer, palliative, and end-of-life care, clinicians should start opioids at the lowest possible effective dosage (the lowest starting dosage on product labeling for patients not already taking opioids and according to product labeling guidance regarding tolerance for patients already taking opioids). Clinicians should use additional caution when initiating opioids for patients aged ≥65 years and for patients with renal or hepatic insufficiency because decreased clearance of drugs in these patients can result in accumulation of drugs to toxic levels. Clinicians should use caution when increasing opioid dosages and increase dosage by the smallest practical amount because overdose risk increases with increases in opioid dosage. Although there is limited evidence to recommend specific intervals for dosage titration, a previous guideline recommended waiting at least five half-lives before increasing dosage and waiting at least a week before increasing dosage of methadone to make sure that full effects of the previous dosage are evident (*31*). Clinicians should re-evaluate patients after increasing dosage for changes in pain, function, and risk for harm (see Recommendation 7). Before increasing total opioid dosage to ≥50 MME/day, clinicians should reassess whether opioid treatment is meeting the patient's treatment goals (see Recommendation 2). 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 considering offering naloxone and overdose prevention education to both patients and the patients' household members (see Recommendation 8). Clinicians should avoid increasing opioid dosages to ≥90 MME/day or should carefully justify a decision to increase dosage to ≥90 MME/day based on individualized assessment of benefits and risks and weighing factors such as diagnosis, incremental benefits for pain and function relative to harms as dosages approach 90 MME/day, other treatments and effectiveness, and recommendations based on consultation with pain specialists. If patients do not experience improvement in pain and function at ≥90 MME/day, or if there are escalating dosage requirements, clinicians should discuss other approaches to pain management with the patient, consider working with patients to taper opioids to a lower dosage or to taper and discontinue opioids (see Recommendation 7), and consider consulting a pain specialist. Some states require clinicians to implement clinical protocols at specific dosage levels. For example, before increasing long-term opioid therapy dosage to >120 MME/day, clinicians in Washington state must obtain consultation from a pain specialist who agrees that this is indicated and appropriate (*30*). Clinicians should be aware of rules related to MME thresholds and associated clinical protocols established by their states.

Established patients already taking high dosages of opioids, as well as patients transferring from other clinicians, might consider the possibility of opioid dosage reduction to be anxiety-provoking, and tapering opioids can be especially challenging after years on high dosages because of physical and psychological dependence. However, these patients should be offered the opportunity to re-evaluate their continued use of opioids at high dosages in light of recent evidence regarding the association of opioid dosage and overdose risk. Clinicians should explain in a nonjudgmental manner to patients already taking high opioid dosages (≥90 MME/day) that there is now an established body of scientific evidence showing that overdose risk is increased at higher opioid dosages. Clinicians should empathically review benefits and risks of continued high-dosage opioid therapy and should offer to work with the patient to taper opioids to safer dosages. For patients who agree to taper opioids to lower dosages, clinicians should collaborate with the patient on a tapering plan (see Recommendation 7). Experts noted that patients tapering opioids after taking them for years might require very slow opioid tapers as well as pauses in the taper to allow gradual accommodation to lower opioid dosages. Clinicians should remain alert to signs of anxiety, depression, and opioid use disorder (see Recommendations 8 and 12) that might be unmasked by an opioid taper and arrange for management of these co-morbidities. For patients agreeing to taper to lower opioid dosages as well as for those remaining on high opioid dosages, clinicians should establish goals with the patient for continued opioid therapy (see Recommendation 2), maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 1), and consider consulting a pain specialist as needed to assist with pain management.

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

The clinical evidence review found that opioid use for acute pain (i.e., pain with abrupt onset and caused by an injury or other process that is not ongoing) is associated with long-term opioid use, and that a greater amount of early opioid exposure is associated with greater risk for long-term use (KQ5). Several guidelines on opioid prescribing for acute pain from emergency departments (*192–194*) and other settings (*195,196*) have recommended prescribing ≤3 days of opioids in most cases, whereas others have recommended ≤7 days (*197*) or <14 days (*30*). Because physical dependence on opioids is an expected physiologic response in patients exposed to opioids for more than a few days (contextual evidence review), limiting days of opioids prescribed also should

minimize the need to taper opioids to prevent distressing or unpleasant withdrawal symptoms. Experts noted that more than a few days of exposure to opioids significantly increases hazards, that each day of unnecessary opioid use increases likelihood of physical dependence without adding benefit, and that prescriptions with fewer days' supply will minimize the number of pills available for unintentional or intentional diversion.

Experts agreed that when opioids are needed for acute pain, clinicians should prescribe opioids at the lowest effective dose and for no longer than the expected duration of pain severe enough to require opioids to minimize unintentional initiation of long-term opioid use. 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 on other clinical factors such as renal or hepatic insufficiency (see Recommendation 8). Experts thought, based on clinical experience regarding anticipated duration of pain severe enough to require an opioid, that in most cases of acute pain not related to surgery or trauma, a ≤3 days' supply of opioids will be sufficient. For example, in one study of the course of acute low back pain (not associated with malignancies, infections, spondylarthropathies, fractures, or neurological signs) in a primary care setting, there was a large decrease in pain until the fourth day after treatment with paracetamol, with smaller decreases thereafter (*198*) Some experts thought that because some types of acute pain might require more than 3 days of opioid treatment, it would be appropriate to recommend a range of ≤3–5 days or ≤3–7 days when opioids are needed. Some experts thought that a range including 7 days was too long given the expected course of severe acute pain for most acute pain syndromes seen in primary care.

Acute pain can often be managed without opioids. It is important to evaluate the patient for reversible causes of pain, for underlying etiologies with potentially serious sequelae, and to determine appropriate treatment. When the diagnosis and severity of nontraumatic, nonsurgical acute pain are reasonably assumed to warrant the use of opioids, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids, often 3 days or less, unless circumstances clearly warrant additional opioid therapy. More than 7 days will rarely be needed. Opioid treatment for post-surgical pain is outside the scope of this guideline but has been addressed elsewhere (*30*). Clinicians should not prescribe additional opioids to patients "just in case" pain continues longer than expected. Clinicians should re-evaluate the subset of patients who experience severe acute pain that continues longer than the expected duration to confirm or revise the initial diagnosis and to adjust management accordingly. Given longer half-lives and longer duration of effects (e.g., respiratory depression) with ER/LA opioids such as methadone, fentanyl patches, or extended release versions of opioids such as oxycodone, oxymorphone, or morphine, clinicians should not prescribe ER/LA opioids for the treatment of acute pain.

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

Although the clinical evidence review did not find studies evaluating the effectiveness of more frequent monitoring intervals (KQ4), it did find that continuing opioid therapy for 3 months substantially increases risk for opioid use disorder (KQ2); therefore, follow-up earlier than 3 months might be necessary to provide the greatest opportunity to prevent the development of opioid use disorder. In addition, risk for overdose associated with ER/LA opioids might be particularly high during the first 2 weeks of treatment (KQ3). The contextual evidence review found that patients who do not have pain relief with opioids at 1 month are unlikely to experience pain relief with opioids at 6 months. 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 minimize risks of long-term opioid use by discontinuing opioids among patients not receiving a clear benefit from these medications. Experts noted that risks for opioid overdose are greatest during the first 3–7 days after opioid initiation or increase in dosage, particularly when methadone or transdermal fentanyl are prescribed; that follow-up within 3 days is appropriate when initiating or increasing the dosage of methadone; and that follow-up within 1 week might be appropriate when initiating or increasing the dosage of other ER/LA opioids.

Clinicians should evaluate patients to assess benefits and harms of opioids within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation. Clinicians should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased or when total daily opioid dosage is ≥50 MME/day. Shorter follow-up intervals (within 3 days) should be strongly considered when starting or increasing the dosage of methadone. At follow up, clinicians should assess benefits in function, pain control, and quality of life using tools such as the three-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale (*186*) and/or asking patients about progress toward functional goals that have meaning for them (see Recommendation 2). Clinicians should also ask patients about common adverse effects such as constipation and drowsiness (see Recommendation 3), as well as asking about and assessing for effects that might be early warning signs for more serious problems such as overdose (e.g., sedation or slurred speech) or opioid use disorder (e.g., craving, wanting to take opioids in greater quantities or more frequently than prescribed, or difficulty controlling use). Clinicians should ask patients about their preferences for continuing opioids, given their effects on pain and function relative to any adverse effects experienced.

Because of potential changes in the balance of benefits and risks of opioid therapy over time, clinicians should regularly reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician but on long-term opioid therapy, at least every 3 months. At reassessment, clinicians should determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function, whether the patient has experienced common or serious adverse events or early warning signs of serious adverse events, signs of opioid use disorder (e.g., difficulty controlling use, work or family problems related to opioid use), whether benefits of opioids continue to outweigh risks, and whether opioid dosage can be reduced or opioids can be discontinued. Ideally, these reassessments would take place in person and be conducted by the prescribing clinician. In practice contexts where virtual visits are part of standard care (e.g., in remote areas where distance or other issues make follow-up visits challenging), follow-up assessments that allow the clinician to communicate with and observe the patient through video and audio could be conducted, with in-person visits occurring at least once per year. Clinicians should re-evaluate patients who are exposed to greater risk of 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. If clinically meaningful improvements in pain and function are not sustained, if patients are taking high-risk regimens (e.g., dosages ≥50 MME/day or opioids combined with benzodiazepines) without evidence of benefit, if patients believe benefits no longer outweigh risks or if

they request dosage reduction or discontinuation, or if patients experience overdose or other serious adverse events (e.g., an event leading to hospitalization or disability) or warning signs of serious adverse events, clinicians should work with patients to reduce opioid dosage or to discontinue opioids when possible. Clinicians should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 1) and consider consulting a pain specialist as needed to assist with pain management.

Considerations for Tapering Opioids

Although the clinical evidence review did not find high-quality studies comparing the effectiveness of different tapering protocols for use when opioid dosage is reduced or opioids are discontinued (KQ3), tapers reducing weekly dosage by 10%–50% of the original dosage have been recommended by other clinical guidelines (*199*), and a rapid taper over 2–3 weeks has been recommended in the case of a severe adverse event such as overdose (*30*). Experts noted that tapers slower than 10% per week (e.g., 10% per month) also might be appropriate and better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations (e.g., for years). Opioid withdrawal during pregnancy has been associated with spontaneous abortion and premature labor.

When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., drug craving, anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should be used. A decrease of 10% of the original dose per week is a reasonable starting point; experts agreed that tapering plans may be individualized based on patient goals and concerns. Experts noted that at times, tapers might have to be paused and restarted again when the patient is ready and might have to be slowed once patients reach low dosages. Tapers may be considered successful as long as the patient is making progress. Once the smallest available dose is reached, the interval between doses can be extended. Opioids may be stopped when taken less frequently than once a day. More rapid tapers might be needed for patient safety under certain circumstances (e.g., for patients who have experienced overdose on their current dosage). Ultrarapid detoxification under anesthesia is associated with substantial risks, including death, and should not be used (*200*). Clinicians should access appropriate expertise if considering tapering opioids during pregnancy because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal. Patients who are not taking opioids (including patients who are diverting all opioids they obtain) do not require tapers. Clinicians should discuss with patients undergoing tapering the increased risk for overdose on abrupt return to a previously prescribed higher dose. Primary care clinicians should collaborate with mental health providers and with other specialists as needed to optimize nonopioid pain management (see Recommendation 1), as well as psychosocial support for anxiety related to the taper. More detailed guidance on tapering, including management of withdrawal symptoms has been published previously (*30*,*201*). If a patient exhibits signs of opioid use disorder, clinicians should offer or arrange for treatment of opioid use disorder (see Recommendation 12) and consider offering naloxone for overdose prevention (see Recommendation 8).

Assessing Risk and Addressing Harms of Opioid Use

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

The clinical evidence review found insufficient evidence to determine how harms of opioids differ depending on patient demographics or patient comorbidities (KQ2). However, based on the contextual evidence review and expert opinion, certain risk factors are likely to increase susceptibility to opioid-associated harms and warrant incorporation of additional strategies into the management plan to mitigate risk. Clinicians should assess these risk factors periodically, with frequency varying by risk factor and patient characteristics. For example, factors that vary more frequently over time, such as alcohol use, require more frequent follow up. In addition, clinicians should consider offering naloxone, re-evaluating patients more frequently (see Recommendation 7), and referring to pain and/or behavioral health specialists when factors that increase risk for harm, such as history of overdose, history of substance use disorder, higher dosages of opioids (≥50 MME/day), and concurrent use of benzodiazepines with opioids, are present.

Patients with Sleep-Disordered Breathing, Including Sleep Apnea

Risk factors for sleep-disordered breathing include congestive heart failure, and obesity. Experts noted that careful monitoring and cautious dose titration should be used if opioids are prescribed for patients with mild sleep-disordered breathing. Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing whenever possible to minimize risks for opioid overdose (contextual evidence review).

Pregnant Women

Opioids used in pregnancy might be associated with additional risks to both mother and fetus. Some studies have shown an association of opioid use in pregnancy with stillbirth, poor fetal growth, pre-term delivery, and birth defects (contextual evidence review). Importantly, in some cases, opioid use during pregnancy leads to neonatal opioid withdrawal syndrome. Clinicians and patients together should carefully weigh risks and benefits when making decisions about whether to initiate opioid therapy for chronic pain during pregnancy. In addition, before initiating opioid therapy for chronic pain for reproductive-age women, clinicians should discuss family planning and how long-term opioid use might affect any future pregnancy. For pregnant women already receiving opioids, clinicians should access appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal (see Recommendation 7). For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine or methadone has been associated with improved maternal outcomes and should be offered (*202*) (see Recommendation 12). Clinicians caring for pregnant women receiving opioids for pain or receiving buprenorphine or methadone for opioid use disorder should arrange for delivery at a facility prepared to monitor, evaluate for, and treat neonatal opioid withdrawal syndrome. In instances when travel to such a facility would present an undue burden on the pregnant woman, it is appropriate to deliver locally, monitor and evaluate the newborn for neonatal opioid withdrawal syndrome, and transfer the newborn for additional

treatment if needed. Neonatal toxicity and death have been reported in breast-feeding infants whose mothers are taking codeine (contextual evidence review); previous guidelines have recommended that codeine be avoided whenever possible among mothers who are breast feeding and, if used, should be limited to the lowest possible dose and to a 4-day supply (*203*).

Patients with Renal or Hepatic Insufficiency

Clinicians should use additional caution and increased monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency, given their decreased ability to process and excrete drugs, susceptibility to accumulation of opioids, and reduced therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (contextual evidence review; see Recommendations 4, 5, and 7).

Patients Aged ≥65 Years

Inadequate pain treatment among persons aged ≥65 years has been documented (*204*). Pain management for older patients can be challenging given increased risks of both nonopioid pharmacologic therapies (see Recommendation 1) and opioid therapy in this population. Given reduced renal function and medication clearance even in the absence of renal disease, patients aged ≥65 years might have increased susceptibility to accumulation of opioids and a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (contextual evidence review). Some older adults suffer from cognitive impairment, which can increase risk for medication errors and make opioid-related confusion more dangerous. In addition, older adults are more likely than younger adults to experience co-morbid medical conditions and more likely to receive multiple medications, some of which might interact with opioids (such as benzodiazepines). Clinicians should use additional caution and increased monitoring (see Recommendations 4, 5, and 7) to minimize risks of opioids prescribed for patients aged ≥65 years. Experts suggested that clinicians educate older adults receiving opioids to avoid risky medication-related behaviors such as obtaining controlled medications from multiple prescribers and saving unused medications. Clinicians should also implement interventions to mitigate common risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.

Patients with Mental Health Conditions

Because psychological distress frequently interferes with improvement of pain and function in patients with chronic pain, using validated instruments such as the Generalized Anxiety Disorder (GAD)-7 and the Patient Health Questionnaire (PHQ)-9 or the PHQ-4 to assess for anxiety, post-traumatic stress disorder, and/or depression (*205*), might help clinicians improve overall pain treatment outcomes. Experts noted that clinicians should use additional caution and increased monitoring (see Recommendation 7) to lessen the increased risk for opioid use disorder among patients with mental health conditions (including depression, anxiety disorders, and PTSD), as well as increased risk for drug overdose among patients with depression. Previous guidelines have noted that opioid therapy should not be initiated during acute psychiatric instability or uncontrolled suicide risk, and that clinicians should consider behavioral health specialist consultation for any patient with a history of suicide attempt or psychiatric disorder (*31*). 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 is optimized, consulting with behavioral health specialists when needed. Treatment for depression can improve pain symptoms as well as depression and might decrease overdose risk (contextual evidence review). For treatment of chronic pain in patients with depression, clinicians should strongly consider using tricyclic or SNRI antidepressants for analgesic as well as antidepressant effects if these medications are not otherwise contraindicated (see Recommendation 1).

Patients with Substance Use Disorder

Illicit drugs and alcohol are listed as contributory factors on a substantial proportion of death certificates for opioid-related overdose deaths (contextual evidence review). Previous guidelines have recommended screening or risk assessment tools to identify patients at higher risk for misuse or abuse of opioids. However, the clinical evidence review found that currently available risk-stratification tools (e.g., Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain Version 1, SOAPP-R, and Brief Risk Interview) show insufficient accuracy for classification of patients as at low or high risk for abuse or misuse (KQ4). Clinicians should always exercise caution when considering or prescribing opioids for any patient with chronic pain outside of active cancer, palliative, and end-of-life care and should not overestimate the ability of these tools to rule out risks from long-term opioid therapy.

Clinicians should ask patients about their drug and alcohol use. Single screening questions can be used (*206*). 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 (*207*). Validated screening tools such as the Drug Abuse Screening Test (DAST) (*208*) and the Alcohol Use Disorders Identification Test (AUDIT) (*209*) can also be used. Clinicians should use PDMP data (see Recommendation 9) and drug testing (see Recommendation 10) as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and overdose. Clinicians should also provide specific counseling on increased risks for overdose when opioids are combined with other drugs or alcohol (see Recommendation 3) and ensure that patients receive effective treatment for substance use disorders when needed (see Recommendation 12).

The clinical evidence review found insufficient evidence to determine how harms of opioids differ depending on past or current substance use disorder (KQ2), although a history of substance use disorder was associated with misuse. Similarly, based on contextual evidence, patients with drug or alcohol use disorders are likely to experience greater risks for opioid use disorder and overdose than persons without these conditions. If clinicians consider opioid therapy for chronic pain outside of active cancer, palliative, and end-of-life care for patients with drug or alcohol use disorders, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone (see Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed. Because pain management in patients

with substance use disorder can be complex, clinicians should consider consulting substance use disorder specialists and pain specialists regarding pain management for persons with active or recent past history of substance abuse. Experts also noted that clinicians should communicate with patients' substance use disorder treatment providers if opioids are prescribed.

Patients with Prior Nonfatal Overdose

Although studies were not identified that directly addressed the risk for overdose among patients with prior nonfatal overdose who are prescribed opioids, based on clinical experience, experts thought that prior nonfatal overdose would substantially increase risk for future nonfatal or fatal opioid overdose. If patients experience nonfatal opioid overdose, clinicians should work with them to reduce opioid dosage and to discontinue opioids when possible (see Recommendation 7). If clinicians continue opioid therapy for chronic pain outside of active cancer, palliative, and end-of-life care in patients with prior opioid overdose, they should discuss increased risks for overdose with patients, carefully consider whether benefits of opioids outweigh substantial risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone (see Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed.

Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present

Naloxone is an opioid antagonist that can reverse severe respiratory depression; its administration by lay persons, such as friends and family of persons who experience opioid overdose, can save lives. Naloxone precipitates acute withdrawal among patients physically dependent on opioids. Serious adverse effects, such as pulmonary edema, cardiovascular instability, and seizures, have been reported but are rare at doses consistent with labeled use for opioid overdose (*210*). The contextual evidence review did not find any studies on effectiveness of prescribing naloxone for overdose prevention among patients prescribed opioids for chronic pain. However, there is evidence for effectiveness of naloxone provision in preventing opioid-related overdose death at the community level through community-based distribution (e.g., through overdose education and naloxone distribution programs in community service agencies) to persons at risk for overdose (mostly due to illicit opiate use), and it is plausible that effectiveness would be observed when naloxone is provided in the clinical setting as well Experts agreed that it is preferable not to initiate opioid treatment when factors that increase risk for opioid-related harms are present. Opinions diverged about the likelihood of naloxone being useful to patients and the circumstances under which it should be offered. However, most experts agreed that clinicians should consider offering naloxone when prescribing opioids to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients taking benzodiazepines with opioids (see Recommendation 11), patients at risk for returning to a high dose to which they are no longer tolerant (e.g., patients recently released from prison), and patients taking higher dosages of opioids (≥50 MME/day). Practices should provide education on overdose prevention and naloxone use to patients receiving naloxone prescriptions and to members of their households. Experts noted that naloxone co-prescribing can be facilitated by clinics or practices with resources to provide naloxone training and by collaborative practice models with pharmacists. Resources for prescribing naloxone in primary care settings can be found through Prescribe to Prevent at http://prescribetoprevent.org (http://prescribetoprevent.org) .

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

PDMPs are state-based databases that collect information on controlled prescription drugs dispensed by pharmacies in most states and, in select states, by dispensing physicians as well. In addition, some clinicians employed by the federal government, including some clinicians in the Indian Health Care Delivery System, are not licensed in the states where they practice, and do not have access to PDMP data. Certain states require clinicians to review PDMP data prior to writing each opioid prescription (see state-level PDMP-related policies on the National Alliance for Model State Drug Laws website at http://www.namsdl.org/prescription-monitoring-programs.cfm (http://www.namsdl.org/prescription-monitoring-programs.cfm)). The clinical evidence review did not find studies evaluating the effectiveness of PDMPs on outcomes related to overdose, addiction, abuse, or misuse (KQ4). However, even though evidence is limited on the effectiveness of PDMP implementation at the state level on prescribing and mortality outcomes (*28*), the contextual evidence review found that most fatal overdoses were associated with patients receiving opioids from multiple prescribers and/or with patients receiving high total daily opioid dosages; information on both of these risk factors for overdose are available to prescribers in the PDMP. PDMP data also can be helpful when patient medication history is not otherwise available (e.g., for patients from other locales) and when patients transition care to a new clinician. The contextual evidence review also found that PDMP information could be used in a way that is harmful to patients. For example, it has been used to dismiss patients from clinician practices (*211*), which might adversely affect patient safety.

The contextual review found variation in state policies that affect timeliness of PDMP data (and therefore benefits of reviewing PDMP data) as well as time and workload for clinicians in accessing PDMP data. In states that permit delegating access to other members of the health care team, workload for prescribers can be reduced. These differences might result in a different balance of benefits to clinician workload in different states. Experts agreed that PDMPs are useful tools that should be consulted when starting a patient on opioid therapy and periodically during long-term opioid therapy. However, experts disagreed on how frequently clinicians should check the PDMP during long-term opioid therapy, given PDMP access issues and the lag time in reporting in some states. Most experts agreed that PDMP data should be reviewed every 3 months or more frequently during long-term opioid therapy. A minority of experts noted that, given the current burden of accessing PDMP data in some states and the lack of evidence surrounding the most effective interval for PDMP review to improve patient outcomes, annual review of PDMP data during long-term opioid therapy would be reasonable when factors that increase risk for opioid-related harms are not present.

Clinicians should review PDMP data for opioids and other controlled medications patients might have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or dangerous combinations (e.g., opioids combined with benzodiazepines) that put him or her at high risk for overdose. Ideally, PDMP data should be reviewed before every opioid prescription. This is recommended in all states with well-functioning PDMPs and where PDMP access policies make this practicable (e.g., clinician and delegate access permitted), but it is not currently possible in states without functional

PDMPs or in those that do not permit certain prescribers to access them. As vendors and practices facilitate integration of PDMP information into regular clinical workflow (e.g., data made available in electronic health records), clinicians' ease of access in reviewing PDMP data is expected to improve. In addition, improved timeliness of PDMP data will improve their value in identifying patient risks.

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

- Clinicians should discuss information from the PDMP with their patient and confirm that the patient is aware of the additional prescriptions. 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).
- Clinicians should discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving opioids from more than one prescriber or receiving medications that increase risk when combined with opioids (e.g., benzodiazepines) and consider offering naloxone (see Recommendation 8).
- Clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible. Clinicians should communicate with others managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care (see Recommendation 11).
- Clinicians should calculate the total MME/day for concurrent opioid prescriptions to help assess the patient's overdose risk (see Recommendation 5). If patients are found to be receiving high total daily dosages of opioids, clinicians should discuss their safety concerns with the patient, consider tapering to a safer dosage (see Recommendations 5 and 7), and consider offering naloxone (see Recommendation 8).
- Clinicians should discuss safety concerns with other clinicians who are prescribing controlled substances for their patient. Ideally clinicians should first discuss concerns with their patient and inform him or her that they plan to coordinate care with the patient's other prescribers to improve the patient's safety.
- Clinicians should consider the possibility of a substance use disorder and discuss concerns with their patient (see Recommendation 12).
- If clinicians suspect their patient might be sharing or selling opioids and not taking them, clinicians should consider urine drug testing to assist in determining whether opioids can be discontinued without causing withdrawal (see Recommendations 7 and 10). A negative drug test for prescribed opioids might indicate the patient is not taking prescribed opioids, although clinicians should consider other possible reasons for this test result (see Recommendation 10).

Experts agreed that clinicians should not dismiss patients from their practice on the basis of PDMP information. Doing so can adversely affect patient safety, could represent patient abandonment, and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of opioids and overdose prevention) and interventions (e.g., safer prescriptions, nonopioid pain treatment [see Recommendation 1], naloxone [see Recommendation 8], and effective treatment for substance use disorder [see Recommendation 12]).

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

Concurrent use of opioid pain medications with other opioid pain medications, benzodiazepines, or heroin can increase patients' risk for overdose. Urine drug tests can provide information about drug use that is not reported by the patient. In addition, urine drug tests can assist clinicians in identifying when patients are not taking opioids prescribed for them, which might in some cases indicate diversion or other clinically important issues such as difficulties with adverse effects. Urine drug tests do not provide accurate information about how much or what dose of opioids or other drugs a patient took. The clinical evidence review did not find studies evaluating the effectiveness of urine drug screening for risk mitigation during opioid prescribing for pain (KQ4). The contextual evidence review found that urine drug testing can provide useful information about patients assumed not to be using unreported drugs. Urine drug testing results can be subject to misinterpretation and might sometimes be associated with practices that might harm patients (e.g., stigmatization, inappropriate termination from care). Routine use of urine drug tests with standardized policies at the practice or clinic level might destigmatize their use. Although random drug testing also might destigmatize urine drug testing, experts thought that truly random testing was not feasible in clinical practice. Some clinics obtain a urine specimen at every visit, but only send it for testing on a random schedule. Experts noted that in addition to direct costs of urine drug testing, which often are not covered fully by insurance and can be a burden for patients, clinician time is needed to interpret, confirm, and communicate results.

Experts agreed that prior to starting opioids for chronic pain and periodically during opioid therapy, clinicians should use urine drug testing to assess for prescribed opioids as well as other controlled substances and illicit drugs that increase risk for overdose when combined with opioids, including nonprescribed opioids, benzodiazepines, and heroin. There was some difference of opinion among experts as to whether this recommendation should apply to all patients, or whether this recommendation should entail individual decision making with different choices for different patients based on values, preferences, and clinical situations. While experts agreed that clinicians should use urine drug testing before initiating opioid therapy for chronic pain, they disagreed on how frequently urine drug testing should be conducted during long-term opioid therapy. Most experts agreed that urine drug testing at least annually for all patients was reasonable. Some experts noted that this interval might be too long in some cases and too short in others, and that the follow-up interval should be left to the discretion of the clinician. Previous guidelines have recommended more frequent urine drug testing in patients thought to be at higher risk for substance use disorder (*30*). However, experts thought that predicting risk prior to urine drug testing is challenging and that currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use disorder.

In most situations, initial urine drug testing can be performed with a relatively inexpensive immunoassay panel for commonly prescribed opioids and illicit drugs. Patients prescribed less commonly used opioids might require specific testing for those agents. The use of confirmatory testing adds substantial costs and should be based on the need to detect specific opioids that cannot be identified on standard immunoassays or on the presence of unexpected urine drug test results. Clinicians should be familiar with the drugs included in urine drug testing panels used in their practice and should understand how to interpret results for these drugs. For example, a positive "opiates" immunoassay detects morphine, which might reflect patient use of morphine, codeine, or heroin, but

this immunoassay does not detect synthetic opioids (e.g., fentanyl or methadone) and might not detect semisynthetic opioids (e.g., oxycodone). However, many laboratories use an oxycodone immunoassay that detects oxycodone and oxymorphone. In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is taking and might not mean the patient is taking the specific opioid for which the test was positive. For example, hydromorphone is a metabolite of hydrocodone, and oxymorphone is a metabolite of oxycodone. Detailed guidance on interpretation of urine drug test results, including which tests to order and expected results, drug detection time in urine, drug metabolism, and other considerations has been published previously (*30*). Clinicians should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. For example, experts noted that there might be uncertainty about the clinical implications of a positive urine drug test for tetrahyrdocannabinol (THC). In addition, restricting confirmatory testing to situations and substances for which results can reasonably be expected to affect patient management can reduce costs of urine drug testing, given the substantial costs associated with confirmatory testing methods. Before ordering urine drug testing, clinicians should have a plan for responding to unexpected results. Clinicians should explain to patients that urine drug testing is intended to improve their safety and should also explain expected results (e.g., presence of prescribed medication and absence of drugs, including illicit drugs, not reported by the patient). Clinicians should ask patients about use of prescribed and other drugs and ask whether there might be unexpected results. This will provide an opportunity for patients to provide information about changes in their use of prescribed opioids or other drugs. Clinicians should discuss unexpected results with the local laboratory or toxicologist and with the patient. Discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit. For example, a patient might explain that the test is negative for prescribed opioids because she felt opioids were no longer helping and discontinued them. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (e.g., gas or liquid chromatography/mass spectrometry) might be warranted to clarify the situation.

Clinicians should use unexpected results to improve patient safety (e.g., change in pain management strategy [see Recommendation 1], tapering or discontinuation of opioids [see Recommendation 7], more frequent re-evaluation [see Recommendation 7], offering naloxone [see Recommendation 8], or referral for treatment for substance use disorder [see Recommendation 12], all as appropriate). If tests for prescribed opioids are repeatedly negative, confirming that the patient is not taking the prescribed opioid, clinicians can discontinue the prescription without a taper. Clinicians should not dismiss patients from care based on a urine drug test result because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids from alternative sources and the clinician missing opportunities to facilitate treatment for substance use disorder.

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

Benzodiazepines and opioids both cause central nervous system depression and can decrease respiratory drive. Concurrent use is likely to put patients at greater risk for potentially fatal overdose. The clinical evidence review did not address risks of benzodiazepine co-prescription among patients prescribed opioids. However, the contextual evidence review found evidence in epidemiologic series of concurrent benzodiazepine use in large proportions of opioid-related overdose deaths, and a case-cohort study found concurrent benzodiazepine prescription with opioid prescription to be associated with a near quadrupling of risk for overdose death compared with opioid prescription alone (*212*). Experts agreed that although there are circumstances when it might be appropriate to prescribe opioids to a patient receiving benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible. In addition, given that other central nervous system depressants (e.g., muscle relaxants, hypnotics) can potentiate central nervous system depression associated with opioids, clinicians should consider whether benefits outweigh risks of concurrent use of these drugs. Clinicians should check the PDMP for concurrent controlled medications prescribed by other clinicians (see Recommendation 9) and should consider involving pharmacists and pain specialists as part of the management team when opioids are co-prescribed with other central nervous system depressants. Because of greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and because tapering opioids can be associated with anxiety, when patients receiving both benzodiazepines and opioids require tapering to reduce risk for fatal respiratory depression, it might be safer and more practical to taper opioids first (see Recommendation 7). Clinicians should taper benzodiazepines gradually if discontinued because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death (contextual evidence review). A commonly used tapering schedule that has been used safely and with moderate success is a reduction of the benzodiazepine dose by 25% every 1–2 weeks (*213*,*214*). CBT increases tapering success rates and might be particularly helpful for patients struggling with a benzodiazepine taper (*213*). If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific anti-depressants or other nonbenzodiazepine medications approved for anxiety should be offered. Experts emphasized that clinicians should communicate with mental health professionals managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.

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

Opioid use disorder (previously classified as opioid abuse or opioid dependence) is defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) as a problematic pattern of opioid use leading to clinically significant impairment or distress, manifested by at least two defined criteria occurring within a year (http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf (http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf)) (*20*).

The clinical evidence review found prevalence of opioid dependence (using DSM-IV diagnosis criteria) in primary care settings among patients with chronic pain on opioid therapy to be 3%–26% (KQ2). As found in the contextual evidence review and supported by moderate quality evidence, opioid agonist or partial agonist treatment with methadone maintenance therapy or buprenorphine has been shown to be more effective in preventing relapse among patients with opioid use disorder (*151–153*). Some studies suggest that using behavioral therapies in combination with these treatments can reduce opioid misuse and increase retention during maintenance therapy and improve compliance after detoxification (*154*,*155*); behavioral therapies are also recommended by clinical

practice guidelines (*215*). The cited studies primarily evaluated patients with a history of illicit opioid use, rather than prescription opioid use for chronic pain. Recent studies among patients with prescription opioid dependence (based on DSM-IV criteria) have found maintenance therapy with buprenorphine and buprenorphine-naloxone effective in preventing relapse (*216*,*217*). Treatment need in a community is often not met by capacity to provide buprenorphine or methadone maintenance therapy (*218*), and patient cost can be a barrier to buprenorphine treatment because insurance coverage of buprenorphine for opioid use disorder is often limited (*219*). Oral or long-acting injectable formulations of naltrexone can also be used as medication-assisted treatment for opioid use disorder in nonpregnant adults, particularly for highly motivated persons (*220*,*221*). Experts agreed that clinicians prescribing opioids should identify treatment resources for opioid use disorder in the community and should work together to ensure sufficient treatment capacity for opioid use disorder at the practice level.

If clinicians suspect opioid use disorder based on patient concerns or behaviors or on findings in prescription drug monitoring program data (see Recommendation 9) or from urine drug 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 (*20*). Alternatively, clinicians can arrange for a substance use disorder treatment specialist to assess for the presence of opioid use disorder. For patients meeting criteria for opioid use disorder, clinicians should offer or arrange for patients to receive evidence-based treatment, usually medication-assisted treatment with buprenorphine or methadone maintenance therapy in combination with behavioral therapies. Oral or long-acting injectable naltrexone, a long-acting opioid antagonist, can also be used in non-pregnant adults. Naltrexone blocks the effects of opioids if they are used but requires adherence to daily oral therapy or monthly injections. For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine (without naloxone) or methadone has been associated with improved maternal outcomes and should be offered (see Recommendation 8). Clinicians should also consider offering naloxone for overdose prevention to patients with opioid use disorder (see Recommendation 8). For patients with problematic opioid use that does not meet criteria for opioid use disorder, experts noted that clinicians can offer to taper and discontinue opioids (see Recommendation 7). For patients who choose to but are unable to taper, clinicians may reassess for opioid use disorder and offer opioid agonist therapy if criteria are met.

Physicians not already certified to provide buprenorphine in an office-based setting can undergo training to receive a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) that allows them to prescribe buprenorphine to treat patients with opioid use disorder. Physicians prescribing opioids in communities without sufficient treatment capacity for opioid use disorder should strongly consider obtaining this waiver. Information about qualifications and the process to obtain a waiver are available from SAMHSA (*222*). Clinicians do not need a waiver to offer naltrexone for opioid use disorder as part of their practice.

Additional guidance has been published previously (*215*) on induction, use, and monitoring of buprenorphine treatment (see Part 5) and naltrexone treatment (see Part 6) for opioid use disorder and on goals, components of, and types of effective psychosocial treatment that are recommended in conjunction with pharmacological treatment of opioid use disorder (see Part 7). Clinicians unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a substance use disorder treatment specialist, such as an office-based buprenorphine or naltrexone treatment provider, or from an opioid treatment program certified by SAMHSA to provide supervised medication-assisted treatment for patients with opioid use disorder. Clinicians should assist patients in finding qualified treatment providers and should arrange for patients to follow up with these providers, as well as arranging for ongoing coordination of care. Clinicians should not dismiss patients from their practice because of a substance use disorder because this can adversely affect patient safety and could represent patient abandonment. Identification of substance 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. In addition, 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 continue to use nonpharmacologic and nonopioid pharmacologic pain treatments as appropriate (see Recommendation 1) and consider consulting a pain specialist as needed to provide optimal pain management.

Resources to help with arranging for treatment include SAMHSA's buprenorphine physician locator (http://buprenorphine.samhsa.gov/bwns_locator (http://buprenorphine.samhsa.gov/bwns_locator)); SAMHSA's Opioid Treatment Program Directory (http://dpt2.samhsa.gov/treatment/directory.aspx (http://dpt2.samhsa.gov/treatment/directory.aspx)); SAMHSA's Provider Clinical Support System for Opioid Therapies (http://pcss-o.org (http://pcss-o.org)), which offers extensive experience in the treatment of substance use disorders and specifically of opioid use disorder, as well as expertise on the interface of pain and opioid misuse; and SAMHSA's Provider's Clinical Support System for Medication-Assisted Treatment (http://pcssmat.org (http://pcssmat.org)), which offers expert physician mentors to answer questions about assessment for and treatment of substance use disorders.

Conclusions and Future Directions

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Clinical guidelines represent one strategy for improving prescribing practices and health outcomes. Efforts are required to disseminate the guideline and achieve widespread adoption and implementation of the recommendations in clinical settings. CDC will translate this guideline into user-friendly materials for distribution and use by health systems, medical professional societies, insurers, public health departments, health information technology developers, and clinicians and engage in dissemination efforts. CDC has provided a checklist for prescribing opioids for chronic pain (http://stacks.cdc.gov/view/cdc/38025 (http://stacks.cdc.gov/view/cdc/38025)), additional resources such as fact sheets (http://www.cdc.gov/drugoverdose/prescribing/resources.html (http://www.cdc.gov/drugoverdose/prescribing/resources.html)), and will provide a mobile application to guide clinicians in implementing the recommendations. CDC will also work with partners to support clinician education on pain management options, opioid therapy, and risk mitigation strategies (e.g., urine drug testing). Activities such as development of clinical decision support in electronic health records to assist clinicians' treatment decisions at the point of care; identification of mechanisms that insurers and pharmacy benefit plan managers can use to promote safer prescribing within plans; and development of clinical quality improvement measures and initiatives to improve prescribing and patient care within health systems have promise for increasing guideline adoption and improving practice. In addition, policy initiatives that address barriers to implementation of the guidelines, such as increasing accessibility of PDMP data within and across states, e-prescribing, and availability of clinicians who can offer medication-assisted treatment for opioid use disorder, are strategies to consider to enhance implementation of the recommended practices. CDC will work with federal partners and payers to evaluate strategies such as payment

reform and health care delivery models that could improve patient health and safety. For example, strategies might include strengthened coverage for nonpharmacologic treatments, appropriate urine drug testing, and medication-assisted treatment; reimbursable time for patient counseling; and payment models that improve access to interdisciplinary, coordinated care.

As highlighted in the forthcoming report on the National Pain Strategy, an overarching federal effort that outlines a comprehensive population-level health strategy for addressing pain as a public health problem, clinical guidelines complement other strategies aimed at preventing illnesses and injuries that lead to pain. A draft of the National Pain Strategy has been published previously (*180*). These strategies include strengthening the evidence base for pain prevention and treatment strategies, reducing disparities in pain treatment, improving service delivery and reimbursement, supporting professional education and training, and providing public education. It is important that overall improvements be made in developing the workforce to address pain management in general, in addition to opioid prescribing specifically. This guideline also complements other federal efforts focused on addressing the opioid overdose epidemic including prescriber training and education, improving access to treatment for opioid use disorder, safe storage and disposal programs, utilization management mechanisms, naloxone distribution programs, law enforcement and supply reduction efforts, prescription drug monitoring program improvements, and support for community coalitions and state prevention programs.

This guideline provides recommendations that are based on the best available evidence that was interpreted and informed by expert opinion. The clinical scientific evidence informing the recommendations is low in quality. To inform future guideline development, more research is necessary to fill in critical evidence gaps. The evidence reviews forming the basis of this guideline clearly illustrate that there is much yet to be learned about the effectiveness, safety, and economic efficiency of long-term opioid therapy. As highlighted by an expert panel in a recent workshop sponsored by the National Institutes of Health on the role of opioid pain medications in the treatment of chronic pain, "evidence is insufficient for every clinical decision that a provider needs to make about the use of opioids for chronic pain" (*223*). The National Institutes of Health panel recommended that research is needed to improve our understanding of which types of pain, specific diseases, and patients are most likely to be associated with benefit and harm from opioid pain medications; evaluate multidisciplinary pain interventions; estimate cost-benefit; develop and validate tools for identification of patient risk and outcomes; assess the effectiveness and harms of opioid pain medications with alternative study designs; and investigate risk identification and mitigation strategies and their effects on patient and public health outcomes. It is also important to obtain data to inform the cost feasibility and cost-effectiveness of recommended actions, such as use of nonpharmacologic therapy and urine drug testing. Research that contributes to safer and more effective pain treatment can be implemented across public health entities and federal agencies (*4*). Additional research can inform the development of future guidelines for special populations that could not be adequately addressed in this guideline, such as children and adolescents, where evidence and guidance is needed but currently lacking. CDC is committed to working with partners to identify the highest priority research areas to build the evidence base. Yet, given that chronic pain is recognized as a significant public health problem, the risks associated with long-term opioid therapy, the availability of effective nonpharmacological and nonopioid pharmacologic treatment options for pain, and the potential for improvement in the quality of health care with the implementation of recommended practices, a guideline for prescribing is warranted with the evidence that is currently available. The balance between the benefits and the risks of long-term opioid therapy for chronic pain based on both clinical and contextual evidence is strong enough to support the issuance of category A recommendations in most cases.

CDC will revisit this guideline as new evidence becomes available to determine when evidence gaps have been sufficiently closed to warrant an update of the guideline. Until this research is conducted, clinical practice guidelines will have to be based on the best available evidence and expert opinion. This guideline is intended to improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death. CDC is committed to evaluating the guideline to identify the impact of the recommendations on clinician and patient outcomes, both intended and unintended, and revising the recommendations in future updates when warranted.

Acknowledgments

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The travel regulations require that "travelers must submit the Travel Expense Reimbursement Voucher with 30 days after completion of their trip". (CAPP Topic 20335, State Travel Regulations, p.7)

In order for the agency to be in compliance with the state travel regulations, please submit your request for today's meeting no later than

February 19, 2018