



**MEDICAL EXAMINING BOARD
CONTROLLED SUBSTANCES COMMITTEE
Room 121A, 1400 East Washington Avenue, Madison
Contact: Tom Ryan (608) 266-2112
April 20, 2016**

The following agenda describes the issues that the Committee plans to consider at the meeting. At the time of the meeting, items may be removed from the agenda. Please consult the meeting minutes for a record of the actions of the Committee.

AGENDA

10:30 A.M. OR IMMEDIATELY FOLLOWING THE FULL BOARD MEETING

OPEN SESSION – CALL TO ORDER – ROLL CALL

A. Adoption of Agenda (1-2)

B. Minutes of December 16, 2015 – Review and Approval (3-4)

C. Administrative Updates

D. Summary of New Opioid Prescribing and Reporting Laws (5-7)

- 1) 2015 Wisconsin Act 269 – Board Review

E. Guidelines Regarding Best Practices in Prescribing Controlled Substances (8-218)

- 1) Review Background Materials
- 2) Guidelines Drafting

F. Legislative Matters, Background Resources and Committee Work Plan Discussion (219-221)

- 1) Proposals for Med 13 Relating to Continuing Medical Education for Prescribing Opioids

G. Deliberation on Items Added After Preparation of Agenda:

- 1) Introductions, Announcements and Recognition
- 2) Election of Committee Officers
- 3) Appointment of Committee Liaison(s)
- 4) Administrative Updates **or** Administrative Matters
- 5) Nominations, Elections, and Appointments
- 6) Education and Examination Matters
- 7) Credentialing Matters
- 8) Practice Matters
- 9) Legislative/Administrative Rule Matters
- 10) Liaison Reports
- 11) Informational Items
- 12) Disciplinary Matters
- 13) Presentations of Petitions for Summary Suspension

- 14) Petitions for Designation of Hearing Examiner
- 15) Presentation of Proposed Stipulations, Final Decisions and Orders
- 16) Presentation of Proposed Final Decision and Orders
- 17) Presentation of Interim Orders
- 18) Petitions for Re-Hearing
- 19) Petitions for Assessments
- 20) Petitions to Vacate Orders
- 21) Requests for Disciplinary Proceeding Presentations
- 22) Motions
- 23) Petitions
- 24) Appearances from Requests Received or Renewed
- 25) Speaking Engagement(s), Travel, or Public Relation Request(s)

H. Public Comments

ADJOURNMENT

**MEDICAL EXAMINING BOARD
CONTROLLED SUBSTANCES COMMITTEE
TELECONFERENCE/VIRTUAL MEETING MINUTES
December 18, 2015**

PRESENT: Rodney Erickson, M.D.; Carolyn Ogland Vukich, M.D.; Sridhar Vasudevan, M.D.; Timothy Westlake, M.D.

EXCUSED: Mary Jo Capodice, D.O.

STAFF: Tom Ryan, Executive Director; Nifty Lynn Dio, Bureau Assistant; and other Department staff

CALL TO ORDER

Tom Ryan, Executive Director, called the meeting to order at 10:43 a.m. A quorum of four (4) members was confirmed.

ADOPTION OF AGENDA

MOTION: Sridhar Vasudevan moved, seconded by Carolyn Ogland Vukich, to adopt the agenda as published. Motion carried unanimously.

ADMINISTRATIVE UPDATES

Election of Committee Officers

COMMITTEE CHAIR

NOMINATION: Sridhar Vasudevan nominated Timothy Westlake for the Office of Committee Chair.

Tom Ryan called for other nominations three (3) times.

Timothy Westlake was elected as Committee Chair by unanimous consent

VICE CHAIR

NOMINATION: Sridhar Vasudevan nominated Rodney Erickson for the Office of Vice Chair.

Tom Ryan called for other nominations three (3) times.

Rodney Erickson was elected as Vice Chair by unanimous consent.

SECRETARY

NOMINATION: Sridhar Vasudevan nominated Carolyn Ogland Vukich for the Office of Secretary.

Tom Ryan called for other nominations three (3) times.

Carolyn Ogland Vukich was elected as Secretary by unanimous consent.

2015 ELECTION RESULTS	
Committee Chair	Timothy Westlake
Vice Chair	Rodney Erickson
Secretary	Carolyn Ogland Vukich

LEGISLATIVE/ADMINISTRATIVE RULE MATTERS

Wis. Admin. Code Chapter MED 13, Relating to Continuing Education for Prescribing Opioids – Rule Writing

MOTION: Sridhar Vasudevan moved, seconded by Timothy Westlake, to recommend to the Full Board a two hour safe and responsible opioid prescribing CME requirement for all licensees. Motion carried unanimously.

MOTION: Sridhar Vasudevan moved, seconded by Timothy Westlake, to request DSPS staff draft a Scope Statement for emergency rules relating to CME, for the Full Board to approve in January 2016. Motion carried unanimously.

ADJOURNMENT

MOTION: Sridhar Vasudevan moved, seconded by Carolyn Ogland Vukich, to adjourn the meeting. Motion carried unanimously.

The meeting adjourned at 12:09 p.m.

**State of Wisconsin
Department of Safety & Professional Services**

AGENDA REQUEST FORM

1) Name and Title of Person Submitting the Request:		2) Date When Request Submitted: 4/6/2016	
		Items will be considered late if submitted after 4:30 p.m. and less than: <ul style="list-style-type: none"> ▪ 10 work days before the meeting for Medical Board ▪ 14 work days before the meeting for all others 	
3) Name of Board, Committee, Council, Sections: Medical Examining Board Controlled Substances Committee			
4) Meeting Date: 4/20/2016	5) Attachments: x Yes <input type="checkbox"/> No	6) How should the item be titled on the agenda page? Summary of New Opioid Prescribing and Reporting Laws	
7) Place Item in: x Open Session <input type="checkbox"/> Closed Session <input type="checkbox"/> Both	8) Is an appearance before the Board being scheduled? If yes, who is appearing? No	9) Name of Case Advisor(s), if required:	
10) Describe the issue and action that should be addressed: Several new laws relating to opioid prescribing and reporting were recently passed by the legislature and signed into law by the Governor. 2015 Wisconsin Act 266 changes the Prescription Drug Monitoring Program (PDMP) reporting period from 7 days to 24 hours. 2015 Wisconsin Act 267 creates reporting requirements for the PDMP to determine the program's effectiveness. 2015 Wisconsin Act 268 requires law enforcement to report instances of inappropriate use of opioids to the PDMP. 2015 Wisconsin Act 269 allows the Medical Examining Board, the Podiatry Affiliated Credentialing Board, the Board of Nursing, the Dentistry Examining Board, and the Optometry Examining Board to issue guidelines regarding best practices in prescribing controlled substances, as defined in s. 961.01 (4), for persons credentialed by that Board who are authorized to prescribe controlled substances. For complete copies of the Acts, go to '2015-16 Session Acts' at http://legis.wisconsin.gov/			
11) Authorization			
Signature of person making this request		Date	
Supervisor (if required)		Date	
Bureau Director signature (indicates approval to add post agenda deadline item to agenda)		Date	

State of Wisconsin



2015 Assembly Bill 660

Date of enactment: **March 17, 2016**

Date of publication*: **March 18, 2016**

2015 WISCONSIN ACT 269

AN ACT *to repeal* 448.05 (6) (at); *to renumber* 440.035; *to amend* 440.035 (title), 448.05 (6) (a), 448.07 (1) (b) and 452.12 (4); and *to create* 227.01 (13) (zk) and 440.035 (2m) of the statutes; **relating to:** guidelines for prescribing controlled substances and the examination authority of the Medical Examining Board.

The people of the state of Wisconsin, represented in senate and assembly, do enact as follows:

SECTION 1. 227.01 (13) (zk) of the statutes is created to read:

227.01 (13) (zk) Are guidelines issued under s. 440.035 (2m).

SECTION 2. 440.035 (title) of the statutes is amended to read:

440.035 (title) General duties and powers of examining boards and affiliated credentialing boards.

SECTION 3. 440.035 of the statutes is renumbered 440.035 (1m).

SECTION 4. 440.035 (2m) of the statutes is created to read:

440.035 (2m) The medical examining board, the podiatry affiliated credentialing board, the board of nursing, the dentistry examining board, or the optometry examining board may issue guidelines regarding best practices in prescribing controlled substances, as defined in s. 961.01 (4), for persons credentialed by that board who are authorized to prescribe controlled substances.

SECTION 5. 448.05 (6) (a) of the statutes, as affected by 2013 Wisconsin Act 240, is amended to read:

448.05 (6) (a) Except as provided in pars. (am), and (ar), ~~and (at)~~, the board shall examine each applicant it

finds eligible under this section in such subject matters as the board deems applicable to the class of license or certificate which the applicant seeks to have granted. Examinations may be both written and oral. In lieu of its own examinations, in whole or in part, the board may make such use as it deems appropriate of examinations prepared, administered, and scored by national examining agencies, or by other licensing jurisdictions of the United States or Canada. The board shall specify passing grades for any and all examinations required.

SECTION 6. 448.05 (6) (at) of the statutes, as created by 2013 Wisconsin Act 240, is repealed.

SECTION 7. 448.07 (1) (b) of the statutes is amended to read:

448.07 (1) (b) The board shall maintain the register required by s. 440.035 (4) (1m) (d), which shall be divided according to the activity for which the registrant is licensed or certified. The board shall make copies available for purchase at cost.

SECTION 8. 452.12 (4) of the statutes is amended to read:

452.12 (4) REGISTER OF BROKERS AND SALESPERSONS. The board shall include in the register the board maintains under s. 440.035 (4) (1m) (d) the names of all brokers and salespersons whose licenses were revoked

* Section 991.11, WISCONSIN STATUTES: Effective date of acts. "Every act and every portion of an act enacted by the legislature over the governor's partial veto which does not expressly prescribe the time when it takes effect shall take effect on the day after its date of publication."

within the past 2 years. The register shall be available for purchase at cost.

**State of Wisconsin
Department of Safety & Professional Services**

AGENDA REQUEST FORM

1) Name and Title of Person Submitting the Request: Nifty Lynn Dio, Bureau Assistant		2) Date When Request Submitted: Items will be considered late if submitted after 12:00 p.m. on the deadline date which is 8 business days before the meeting	
3) Name of Board, Committee, Council, Sections: Controlled Substances Committee of the Medical Examining Board			
4) Meeting Date: 04/20/2016	5) Attachments: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	6) How should the item be titled on the agenda page? Guidelines Regarding Best Practices in Prescribing Controlled Substances 1. Review Background Materials 2. Guidelines Drafting	
7) Place Item in: <input checked="" type="checkbox"/> Open Session <input type="checkbox"/> Closed Session	8) Is an appearance before the Board being scheduled? <input type="checkbox"/> Yes (Fill out Board Appearance Request) <input checked="" type="checkbox"/> No	9) Name of Case Advisor(s), if required:	
10) Describe the issue and action that should be addressed:			
11) Authorization			
Nifty Lynn Dio			
Signature of person making this request		Date	
Supervisor (if required)		Date	
Executive Director signature (indicates approval to add post agenda deadline item to agenda)		Date	
Directions for including supporting documents: 1. This form should be attached to any documents submitted to the agenda. 2. Post Agenda Deadline items must be authorized by a Supervisor and the Policy Development Executive Director. 3. If necessary, provide original documents needing Board Chairperson signature to the Bureau Assistant prior to the start of a meeting.			



March 28, 2016

Mr. Jeffrey Marcus, Safety Recommendation Specialist
National Transportation Safety Board
correspondence@ntsb.gov

Dear Mr. Marcus:

Recently, Chairman Christopher Hart sent a letter dated November 12, 2015 to Governor Scott Walker requesting information on several recommendations made by the National Transportation Safety Board (NTSB) regarding the use of controlled substances.

Regarding recommendation I-14-1, the Wisconsin State Legislature passed a law, effective March 19, 2016, allowing the Medical Examining Board, Podiatry Affiliated Credentialing Board, Dentistry Examining Board, Board of Nursing and Optometry Examining Board to each write guidelines regarding best practices in prescribing controlled substances. The NTSB Safety Recommendations will be made available to the boards as they develop guidelines for practitioners authorized to prescribe.

Regarding recommendation I-14-2, a link will be established on the Department website so that prescribers and dispensers in Wisconsin have access to the NTSB Safety Recommendations and are reminded of the importance of routinely discussing the effects of prescribed medications.

Thank you for your interest in this matter.

Sincerely,

Greg Gasper
Administrator, Division of Policy Development

cc: Michael Berndt, Chief Legal Counsel
Tom Ryan, Executive Director
Dan Williams, Executive Director
Brittany Lewin, Executive Director



Office of the Chairman

National Transportation Safety Board

Washington, DC 20594

November 12, 2015

The Honorable Scott Walker
Governor of Wisconsin
Office of the Governor
115 East Capitol
Madison, WI 53702

Dear Governor Walker:

The National Transportation Safety Board (NTSB) is an independent federal agency charged by Congress with investigating every civil aviation accident in the United States and significant accidents in other modes of transportation—railroad, highway, marine, and pipeline. We determine the probable cause of the accidents and issue safety recommendations aimed at preventing future accidents. In addition, we conduct special studies concerning transportation safety and coordinate the resources of the federal government and other organizations to provide assistance to victims and their family members impacted by major transportation disasters.

This letter addresses NTSB Safety Recommendations I-14-1 and -2. We issued these recommendations to the state of Wisconsin on September 23, 2014, as a result of our safety study *Drug Use Trends in Aviation: Assessing the Risk of Pilot Impairment*, SS 14/01, available at <http://www.nts.gov/safety/safety-studies/Documents/SS1401.pdf>. For your convenience, the background and bases for the recommendations may be found on pages 36-38 of the report.

I-14-1

Include in all state guidelines regarding prescribing controlled substances for pain a recommendation that health care providers discuss with patients the effect their medical condition and medication use may have on their ability to safely operate a vehicle in any mode of transportation.

I-14-2

Use existing newsletters or other routine forms of communication with licensed health care providers and pharmacists to highlight the importance of routinely discussing with patients the effect their diagnosed medical conditions or recommended drugs may have on their ability to safely operate a vehicle in any mode of transportation.

We are interested in knowing whether and how our recommendations are implemented, both to ensure that the traveling public is provided the highest level of safety and to identify creative solutions that might be shared with others, and we normally expect actions to address our recommendations to be completed within 3 to 5 years. As we issued this recommendation more than a year ago and we have yet to hear from you regarding it, we would appreciate receiving a response within 90 days indicating actions you have taken or plan to take to implement it. In the meantime, the recommendation will retain its current classification of “Open—Await Response.”

Please reply at correspondence@ntsb.gov. If your response, including attachments, exceeds 10 megabytes, please e-mail us at the same address for instructions. Please do not submit both an electronic and a hard copy of the same response.

If you have any questions, please contact Mr. Jeffrey Marcus, Safety Recommendation Specialist, at marcusj@ntsb.gov.

Thank you for your assistance in this matter.

Sincerely,

cc: Mr. Thomas Ryan
Executive Director
Wisconsin Medical Examining Board
thomas.ryan@wisconsin.gov

Mr. Dan Williams
Bureau Director
Wisconsin Department of Safety and
Professional Services
dsps@wisconsin.gov

Mr. Dan Williams
Executive Director
Wisconsin Pharmacy Examining Board
dsps@wisconsin.gov

CDC Guideline for Prescribing Opioids for Chronic Pain, 2016

Contributing Authors:

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Summary

This guideline provides recommendations for primary care providers who are prescribing opioids for chronic pain outside of end-of-life care. The guideline addresses (1) when to initiate or continue opioids for chronic pain outside of end-of-life care; (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, basing recommendations on a systematic review of the scientific evidence, while considering benefits and harms, values and preferences, and resource implications. CDC consulted with experts knowledgeable in the areas of opioid prescribing, addiction, substance use disorder treatment, and pain management to inform the recommendations, and provided opportunities for stakeholder review and public engagement. It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. These recommendations are intended to promote safer use of opioids to improve clinical practice, patient outcomes, and public health.

Introduction

Background and Objective

Opioids are commonly prescribed for pain. An estimated 20% of patients presenting to physician offices with pain symptoms or diagnoses receive an opioid prescription (1). In 2012, health care providers wrote 259 million prescriptions for opioid pain medication – enough for every American adult to have a bottle of pills (2). Opioid prescriptions per capita increased 7.3% from 2007 to 2012, with prescribing rates for family practice, general practice, and internal medicine increasing more than the average opioid rate of growth (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 on how to use opioid pain medication (2).

Prevention, assessment, and treatment of chronic pain is a challenge for health providers and systems (4). It is important that patients receive appropriate pain treatment based on a careful consideration of the benefits and risks of treatment options. The number of people experiencing chronic pain in the United States is substantial. Chronic pain has been variously defined but is considered within this guideline as pain that typically lasts longer than 3 months or past the time of normal tissue healing (5). Chronic pain can be the result of an underlying medical disease or condition, an injury, medical treatment, inflammation, or unknown cause (4). Estimates of the prevalence of chronic pain vary. The National Health and Nutrition Examination Survey estimated a prevalence of current widespread or localized pain lasting at least 3 months of 14.6% (6). The overall prevalence of common, predominantly musculoskeletal pain conditions that can be chronic (e.g., arthritis, rheumatism, chronic back or neck problems, frequent severe headaches) is estimated at 43% among adults in the United States (7). Most recently, analysis of data from the 2012 National Health Interview Study revealed an estimated prevalence of daily (chronic) pain of 11.2% (8). Yet, the presence of a significant proportion of individuals with chronic pain or painful conditions does not imply that opioid pain medications are the optimal course of treatment for all these

individuals. The number of people who could potentially benefit from opioid pain medication long term is difficult to estimate. Although evidence supports short-term efficacy of opioids for reducing non-cancer nociceptive and neuropathic pain lasting < 16 weeks (9), there is a lack of studies on long-term benefits of opioids for chronic pain (pain lasting > 3 months) with outcomes examined at least 1 year later (10). Based on recent data available from health systems, it is estimated that 9.6 to 11.5 million adults, or approximately 3-4% of the adult US population, are prescribed long-term (chronic) opioid therapy (11).

Unfortunately, there are serious risks of opioid pain medication use, including opioid use disorder (opioid dependence or abuse) and overdose. In 2013, more than 16,000 persons died from overdose related to opioid pain medication in the United States, four times the number who died from overdoses related to these drugs in 1999 (12). Sales of opioid pain medication have increased in parallel with overdose deaths (13). In 2013, an estimated 1.9 million persons abused or were dependent on prescription opioid pain medication (14). Having a history of an opioid prescription is one of many factors that increase risk for overdose and opioid use disorder (15-17), suggesting the importance of guidance on safer prescribing practices for providers.

The objective of this guideline is to provide new recommendations for the prescribing of opioid pain medication by primary care providers for chronic pain (i.e., pain conditions that typically last longer than 3 months or past the time of normal tissue healing) in outpatient settings outside of end-of-life care (e.g., hospice care). While the guideline does not focus broadly on pain management, appropriate use of long-term opioid therapy must be considered within the context of pain management strategies (including non-opioid pain medications and non-pharmacologic treatments). The guideline outlines strategies for safer use of opioid pain medication for chronic pain. Recommendations are based on a systematic review of the best available evidence, with consultation from an expert panel. Improving the way opioid pain medications are prescribed for chronic pain through clinical practice guidelines is intended to ensure patients have access to safer, more effective treatment while reducing the number of persons who develop opioid use disorder, overdose, or experience adverse events related to these drugs.

Rationale

Primary care providers report concern about opioid pain medication misuse, find managing patients with chronic pain stressful, express worry about patient addiction, and report insufficient training in prescribing opioids (18). Across specialties, physicians agree that while opioid pain medication can be effective in controlling pain, physical dependence, tolerance, and addiction are consequences of prolonged use; long-term opioid therapy is often overprescribed for patients with chronic non-cancer pain; and overprescribing will decrease the effectiveness of the medication in relieving pain (19). These attitudes and beliefs combined with increasing trends in opioid use disorder and overdose associated with opioid pain medication underscore the need for better provider guidance on opioid prescribing. Clinical practice guidelines focused on prescribing can improve provider knowledge, change prescribing practices, (20) and ultimately benefit patient health.

Professional organizations, states, and federal agencies have developed guidelines on opioid prescribing (e.g., the American Pain Society/American Academy of Pain Medicine, 2009; Washington Agency Medical Directors Group, 2015; and the US Department of Veteran Affairs/Department of Defense, 2010). (21-23). There are some common elements across existing guidelines, including dosing thresholds, cautious titration, and risk mitigation strategies such as risk assessment tools, treatment agreements, and urine drug testing. However, there is considerable variability in the specific recommendations (e.g., dosing threshold of 90 morphine milligram equivalents (MME)/day versus 200 MME/day), audience (e.g., primary care versus specialists), use of evidence (e.g., systematic review versus expert opinion), and rigor of methods for addressing conflict of interest (see Nuckols et al. for a review (24)). Most guidelines, especially those that are not based on scientific studies published in 2010 or later, also do not reflect the most recent scientific evidence about risks related to opioid dosage.

New CDC guidelines can offer clarity on recommendations based on the most recent scientific evidence. Development of clinical practice guidelines with public funding decreases the likelihood of conflicts of interest

that can result in commercial influence and bias. CDC has a unique role in providing to healthcare professionals data and evidence-based guidance and tools that can improve both clinical and public health practice. 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, extended-release/long-acting (ER/LA) opioids for acute pain) (17, 25, 26). Addressing problematic prescribing through guidelines has the potential to result in optimization of care and improvements in patient safety based on evidence-based practice (20), as well as potentially disrupt the cycle of opioid pain medication misuse and abuse that contribute to the overdose epidemic. Because of CDC's reach, CDC recommendations for primary care practitioners can be efficiently translated and disseminated for rapid adoption into practice.

Scope and Audience

This guideline is intended for primary care providers (e.g. family physicians, internists) who are treating patients for chronic pain in outpatient settings. Primary care providers account for nearly half of all dispensed opioid prescriptions and have experienced above-average growth in prescribing rates (3). This guideline is intended to apply to patients aged ≥ 18 years with chronic pain (i.e., pain lasting longer than 3 months or past the time of normal tissue healing) outside of end-of-life care (e.g., hospice care). The guideline is not intended for 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 palliative care. Patients include those with chronic pain, regardless of whether they have a current or previous diagnosis of cancer. Use of opioid pain medication with special populations (e.g. older adults, pregnant women) and in populations with conditions posing special risks (e.g., substance use disorder) is addressed within the recommendations.

The recommendations are not intended for guiding use of opioid pain medication as part of medication-assisted treatment for substance use disorders. Some of the recommendations might be relevant for acute care settings, but use in these settings is not the focus of this guideline. Readers are referred to other sources for prescribing recommendations within these settings, such as the American College of Emergency Physicians' guideline for prescribing of opioids in the emergency department, the American Society of Anesthesiologists' guideline for acute pain management in the perioperative setting, and the Washington Agency Medical Directors' Group Interagency Guideline on Prescribing Opioids for Pain, Part II: Prescribing Opioids in the Acute and Subacute Phase (23, 27, 28). In addition, management of acute pain emergencies associated with chronic conditions such as vaso-occlusive crisis in sickle cell disease is not a focus of this guideline. 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 painful complications of sickle cell disease (29).

Guideline Development Methods

Guideline Development Using GRADE

CDC developed this guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (<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 grades the overall quality of each body of evidence as high, moderate, low, or very low. Studies using randomized designs are initially rated as high quality, and observational studies are rated as low quality. Quality ratings change 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. The method grades recommendations as strong or weak. Four major factors determine the strength of recommendations: the quality of evidence, the balance between desirable and undesirable effects, values and preferences, and costs. Strong recommendations indicate that most patients should receive the recommended course of action and the recommendation could be adopted as policy in most situations. Weak recommendations indicate that different choices will be appropriate for different patients, such that providers must help patients arrive at a decision

consistent with patient values, preferences, and specific clinical situations; policy making often requires substantial debate and stakeholder involvement (30). For an extensive discussion of GRADE methodology, see the six-part BMJ journal series (30) or the twenty-part Journal of Clinical Epidemiology series on the approach to systematic review and guideline development (31).

A previously published Agency for Healthcare Research and Quality (AHRQ)-sponsored systematic review on *The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain* (10, 32) served as an initial foundation 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 effort, 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 (see the Clinical Evidence Review section below and Online Appendix 1 for more detail). CDC developed GRADE evidence tables to illustrate the strength of the evidence for each clinical question.

As identified in the AHRQ-sponsored clinical evidence review, the evidence base regarding the effectiveness and risks of long-term opioid treatment is rated as low in quality. Thus, contextual evidence that provides information about alternatives to long-term opioid therapy and the epidemiology of opioid pain medication overdose is critical for informing the recommendations. Further, as elucidated by the GRADE Working Group, supplemental information on provider and patient values and preferences, and cost efficiency 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, focusing on the following four areas: effectiveness of alternative treatments (i.e., non-pharmacologic and non-opioid pharmacologic treatments); benefits and harms related to opioid therapy (found in epidemiology rather than the clinical randomized trial literature related to specific opioid pain medications, high-dose opioid therapy, co-prescription of opioids with other controlled substances, duration of opioid use, special populations, and risk stratification/mitigation approaches); provider and patient values and preferences; and resource implications. CDC constructed narrative summaries of this contextual evidence and used the information to support the clinical recommendations (see the Contextual Evidence Review section below and Online Appendix 2 for more detail).

Based on a review of the clinical and contextual evidence (review methods described in more detail below), CDC drafted recommendation statements focusing on determining when to initiate or continue opioids for chronic pain outside of end-of-life care; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. CDC then solicited expert opinion in the form of individual ratings, discussions, and written comment to inform a refinement of the recommendations.

Solicitation of Expert Opinion

CDC recruited a Core Expert Group (CEG) to assist in interpreting the evidence and translating the evidence into recommendations. Group members provided individual consultation and were not part of a designated Federal Advisory Committee. The CEG consisted of subject matter experts, primary care professional society representatives, state agency representatives, and an expert in guideline development methodology (see Appendix A for a list of CEG members). CDC identified subject matter experts with high scientific standing; appropriate academic training and relevant experience; and proven scientific excellence in opioid prescribing, addiction, substance use disorder treatment, and pain management. CDC identified representatives from leading primary care professional organizations to represent the target audience for this guideline. Finally, CDC identified state agency 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. In selecting members, CDC aimed to minimize conflict of interest, enhance objective assessment of the evidence, and reduce bias.

For a guideline to be credible, it is important to eliminate or effectively manage sources of bias. These sources of bias might include financial relationships with industry, intellectual preconceptions, and previously stated public positions. Prior to participation, CDC asked CEG members to reveal potential conflicts of interest. Members could not serve if they held conflicts that could be anticipated to have a direct and predictable effect on the recommendations. CDC excluded persons with conflicts of interest from the CEG, particularly persons with a financial or promotional relationship with a company that makes a product that might be affected by the guideline (e.g., conflicts related to employment and consulting, research support, and financial investments). CDC reviewed potential non-financial 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. Thus, all CEG members 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 in Appendix B.

The CEG reviewed summaries of the scientific evidence and CDC's draft recommendation statements. CEG members provided individual ratings for each draft recommendation statement based on the balance of benefits and risks, evidence strength, certainty of values and preferences, cost, recommendation strength, rationale, importance, clarity, and ease of implementation. CDC convened CEG members at an in-person meeting June 23-24, 2015 in Atlanta, GA to discuss the evidence and recommendations and obtain expert opinions. The CEG provided individual opinions at the meeting within a group discussion; no formal voting consensus processes were used. At the meeting, CDC noted CEG members' comments and any dissenting opinions on the recommendations. CEG members also reviewed the final guideline document and provided written comments for consideration by CDC.

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 federal partners to observe the CEG meeting and provide comment on the recommendations after the meeting. Interagency collaboration will be critical for translation of these recommendations into clinical practice. Federal partners included representatives from the Substance Abuse and Mental Health Services Administration, National Institute on Drug Abuse, FDA, US Department of Veterans Affairs, US Department of Defense, Office of the National Coordinator for Health Information Technology, Centers for Medicare and Medicaid Services, National Institute of Occupational Safety and Health, 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 designated a Stakeholder Review Group (SRG) to provide comment so that CDC could consider modifications that would improve the specificity, applicability, and implementability of the recommendations. The SRG included representatives from professional organizations that represent specialties that commonly prescribe opioids (e.g., pain medicine, physical medicine and rehabilitation) as well as delivery systems within which opioid prescribing occurs (e.g., hospitals). The group also included representation from community organizations with interests in pain management and opioid prescribing. For a full list of the SRG members, see Appendix C. CDC identified representatives from each of the SRG organizations and provided a copy of the guideline for comment. Once input is received by the full SRG, CDC will review comments and make revisions to the guideline prior to finalization.

Peer Review

Peer review requirements applied to this guideline because they provide influential scientific information that could have a clear and substantial impact on public and private sector decisions. Three experts will independently peer review the guideline to determine the reasonableness of recommendations and ensure that scientific

uncertainties are clearly identified. CDC selected peer reviewers based on expertise and diversity of scientific viewpoints, while addressing conflict of interest concerns and ensuring independence from the guideline development process. CDC placed the names of peer reviewers on the CDC and the National Center for Injury Prevention and Control Peer Review Agenda. CDC will review peer reviewer comments and will revise the guideline prior to finalization.

Public Engagement

To obtain perspectives from the public, including providers and prospective patients, CDC will convene a public engagement webinar and circulated information about the webinar in advance through announcements to partners. CDC will host the webinar on September 16, 2015 and will provide information about the methodology for developing the guideline and present the key recommendations. CDC will solicit comments during this open forum and will revise the guideline in response.

Clinical Evidence Review

Primary Clinical Questions

For this guideline, CDC addressed five primary clinical questions regarding the effectiveness, benefits, and harms of opioids for chronic pain through systematic reviews of the scientific evidence. A previously published AHRQ-funded systematic review on the effectiveness and risks of long-term opioid treatment of chronic pain comprehensively addressed four clinical questions (10, 32). CDC, with the assistance of a methodology expert, searched the literature to identify newly published studies on these four original questions. CDC subsequently developed a fifth clinical question and in collaboration with a methodologist conducted a systematic review of the scientific evidence to address it. In brief, the five clinical questions addressed:

1. The effectiveness of long-term opioid therapy versus placebo, no opioid therapy, or non-opioid 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 1; KQ1);
2. 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);
3. The comparative effectiveness of opioid dosing strategies (different methods for initiating and titrating opioids; short-acting versus ER/LA opioids; different ER/LA opioids; short-acting 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);
4. The accuracy of instruments for predicting risk of 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 of opioid overdose, addiction, abuse, or misuse; and the comparative effectiveness of treatment strategies for managing patients with addiction (KQ4); and
5. The effects of prescribing opioid therapy versus not prescribing opioid therapy for acute pain on long-term use (KQ5).

A detailed listing of the key questions can be found in Online Appendix 1.

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 (10, 32). Study authors developed the protocol using a standardized process (33) with input from experts and the public and registered the protocol in the PROSPERO database (34). CDC conducted an updated literature search using the same search strategies as in the original review. Seven additional studies met inclusion criteria and were added to the review. 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 can be found in Online Appendix 1.

Summary of Findings for Clinical Questions

Main findings of this updated review are consistent with the findings of the 2014 AHRQ report (10). 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, though evidence suggests risk of serious harms that appears to be dose-dependent.

The Table shows the GRADE evidence summary with levels of evidence ratings for the five clinical questions. 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 available in the full 2014 AHRQ report (10, 32). Full details on the clinical evidence review findings supporting this guideline can be found in Online Appendix 1.

Effectiveness

For KQ1, no study of opioid therapy versus placebo, no opioid therapy, or non-opioid therapy for chronic pain evaluated long-term (>1 year) outcomes related to pain, function, or quality of life. Most placebo-controlled randomized trials were ≤ 6 weeks in duration. Thus, the quality of evidence for KQ1 is very low (0 studies contributing) (10).

Harms

For KQ2, the quality of evidence is low (12 studies contributing; 11 from the original review plus one new study). One fair-quality cohort study found long-term opioid therapy is associated with increased risk of an opioid abuse or dependence diagnosis versus no opioid prescription (15). Rates of opioid abuse or dependence ranged from 0.7% with low-dose chronic therapy to 6.1% with high-dose chronic therapy, versus 0.004% with no opioids. Ten fair-quality uncontrolled studies reported estimates of opioid abuse, addiction, and related outcomes (35-45). In primary care settings, prevalence of opioid dependence (using DSM-IV criteria) ranged from 3% to 26% (35, 36, 39). In pain clinic settings, prevalence of addiction ranged from 2% to 14% (37, 38, 40, 41, 43-45).

Factors associated with increased risk of misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications (36, 42). Two studies reported on the association between opioid use and risk of overdose (46, 47). One large, fair-quality retrospective cohort study found recent opioid use was associated with increased risk of any overdose events and serious overdose events versus non-use (46). It also found higher doses associated with increased risk. Relative to 1 to 19 MME/day, the adjusted hazard ratio (HR) for an overdose was 1.44 for 20 to 49 MME/day, 3.73 for 50 to 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 of overdose (47). Relative to 1 to 19 MME/day, the adjusted odds ratio (OR) was 1.32 for 20 to 49 MME/day, 1.92 for 50 to 99 MME/day, 2.04 for 100 to 199 MME/day, and 2.88 for ≥ 200 MME/day.

Findings of increased fracture risk for current opioid use, versus non-use, were mixed in two studies (48, 49). Two studies found an association between opioid use and increased risk of cardiovascular events (50, 51). 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 new newly reviewed study) (52, 53). One study found opioid dosages ≥ 20 MME/day associated with increased odds of road trauma among drivers (54).

Opioid Dosing Strategies

For KQ3, the quality of evidence is very low (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 short-acting opioids for titrating patients to stable pain control (55, 56). One new fair-quality cohort study of Veterans Affairs patients found initiation of therapy with an ER/LA opioid associated with greater risk of nonfatal overdose than initiation with a short-acting opioid, with risk greatest in the first 2 weeks after initiation of treatment (57).

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 (58-60), but had methodological shortcomings. A fair-quality retrospective cohort study based on national Veterans Affairs system pharmacy data found methadone associated with lower overall risk of all-cause mortality versus morphine (61) and a fair-quality retrospective cohort study based on Oregon Medicaid data found no statistically significant differences between methadone versus long-acting morphine in risk of death or overdose symptoms (62). However, a new observational study (63) found methadone associated with increased risk of 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 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 versus maintenance of current doses after 12 months in pain, function, all-cause withdrawals, or withdrawals due to opioid misuse (64). 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 short-acting opioids; short-acting 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 (65-67).

Risk Assessment and Mitigation

For KQ4, the quality of evidence is low or very low (six studies contributing; four from the original review plus two new studies). The 2014 AHRQ report included four studies (68-71) 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) (69-71) were extremely inconsistent; evidence for other risk assessment instruments was very sparse, and studies had serious methodological shortcomings. One additional fair-quality (72) and one poor-quality (73) 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 non-informative (positive likelihood ratio close to 1) to moderately useful (positive likelihood ratio >5). The SOAPP-R was associated with non-informative 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 quality of evidence is low (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 (74). Use of opioids within 7 days of surgery was associated with increased risk of use at 1 year. The other study found early opioid use (defined as use within 15 days following onset of pain) among patients with a workers' compensation claim for acute low back pain associated with an increased likelihood of receiving five or more opioid prescriptions 30 to 730 days following onset versus non-use that increased with greater early exposure (75).

Contextual Evidence Review

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 alternative treatments, including non-pharmacologic (e.g., cognitive behavioral therapy [CBT], exercise therapy, interventional treatments, multimodal pain treatment) and non-opioid pharmacologic treatments (e.g., acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], antidepressants, anticonvulsants);
- Benefits and harms of opioid therapy, including findings from the epidemiology and public health literature (rather than the clinical trial literature included in the clinical evidence review) 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;
- Provider and patient values and preferences related to opioids and medication risks, benefits, and use; and
- Resource implications 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 alternative treatments; guidelines with recommendations related to specific provider actions such as urine drug testing or opioid tapering protocols).

Contextual Evidence Review Methods

CDC conducted “rapid reviews” of the contextual evidence on alternative treatments, benefits and harms, values and preferences, and resource implications. Rapid reviews are used when there is a need to streamline the systematic review process to obtain evidence in a short time frame (76). Methods used to streamline the process include limiting searches by databases, years, and languages considered, and truncating quality assessment and data abstraction protocols. Given the public health urgency of developing opioid prescribing recommendations, a rapid review was required for the current guideline.

Detailed information about contextual evidence data sources and searches, inclusion criteria, study selection, and data extraction and synthesis are available in Online Appendix 2. 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 was not systematically searched. Database sources varied by topic, including MEDLINE,

PsycINFO, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. Multiple reviewers scanned study abstracts identified through the database searches, and abstracted relevant studies for review. CDC constructed narrative summaries and tables based on relevant articles that met inclusion criteria.

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. The studies that addressed benefits and harms, values and preferences, and resource implications 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.

Summary of Findings for Contextual Areas

Readers will find full narrative reviews and tables that summarize key findings from the contextual evidence review in Online Appendix 2.

Effectiveness of Alternative Treatments

Several non-pharmacologic and non-opioid pharmacologic treatments have been shown to be effective in managing chronic pain. For example, cognitive-behavioral therapy (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 catastrophizing (77). Exercise therapy can improve pain and function in chronic low back pain (78), improve function and reduce pain in osteoarthritis of the knee (79) and hip (80), and improve well-being, fibromyalgia symptoms, and physical function in fibromyalgia (81). Multimodal integrative therapies (e.g., therapies that pair relaxation approaches with CBT or exercise) can sometimes have more positive effects than single modalities (82). Non-opioid 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 NSAIDs as first-line pharmacotherapy for osteoarthritis (83-88) or for low back pain (89); however, NSAIDs and COX-2 inhibitors do have gastrointestinal, renal, and cardiovascular risks. The FDA has recently strengthened existing label warnings that NSAIDs increase risks for heart attack and stroke, including that these risks may increase with longer use or at higher doses (90). Several guidelines agree that first and second-line drugs for neuropathic pain include anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, and SNRIs (91-94). Interventional approaches such as epidural injection for certain conditions (e.g., lumbar radiculopathy) can provide short-term improvement in pain and in function that can facilitate exercise therapy. However, evidence has not demonstrated long-term benefit, and epidural injection has been associated with rare but serious adverse events, including loss of vision, stroke, paralysis, and death (95).

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/mitigation approaches. Additional information on benefits and harms of long-term opioid therapy from studies meeting rigorous selection criteria can be found 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 are presented in the background section of this document, with detailed information presented in Online Appendix 2.

Regarding specific opioids and formulations, as noted by the U.S. Food and Drug Administration, 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 and for which alternative treatment options are inadequate (96). Time-scheduled opioid use was associated with substantially higher average daily opioid

dosage than as-needed opioid use in one study (97). 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 in states that participated in the Drug Abuse Warning Network, despite representing < 2% of opioid prescriptions outside of opioid treatment programs in the United States (98).

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 (16, 17, 99-101). 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 (16, 17) as well as the two studies in the clinical evidence review (102, 103) 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 non-malignant pain was between 1.3 (103) and 1.9 (17) for dosages of 20 to less than 50 MME/day, between 1.9 (103) and 4.6 (17) for dosages of 50 to less than 100 MME/day, and between 2.0 (103) and 8.9 (102) for dosages of at least 100 MME/day. A recent study of Veterans Health Administration patients with chronic pain (103) 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). 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 (104).

Regarding co-prescription 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 (103-105). In one of these studies (103), 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 (106). Patients who do not experience clinically meaningful pain relief early in treatment (e.g., within 1 month) are unlikely to experience pain relief with longer term use (107).

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 due to the types of study designs and methods employed, and there is not clear consensus regarding development of obstructive sleep apnea syndrome (108). 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 (109), 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) (22). Reduced renal and/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 (110). Age-related changes in patients \geq 65 years such as reduced renal function and medication clearance, even in the absence of renal disease (111), 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 fracture related to opioids (112-114). Opioids used in pregnancy can be associated with additional risks to both mother and fetus. Opioid treatment during pregnancy has been found to be associated with birth defects (neural tube defects (115, 116) congenital heart defects (116), and gastroschisis (116)), pre-term delivery (117), poor fetal growth (117), stillbirth (117), and neonatal abstinence syndrome (118). Patients with mental health co-morbidities and patients with histories of substance use disorders might be at higher risk than other patients for opioid use disorder (119-121). 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 (122). In case-control and case-cohort studies, frequency of substance abuse/dependence was more prevalent among patients experiencing overdose than among patients not experiencing overdose (12% versus 6% (102), 40% versus 10% (17), 26% versus 9% (16)).

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 retrospectively identified based on two pieces of information (multiple prescribers and high total daily opioid dosage, both important risk factors for overdose (99, 123)) that are available to prescribers in the PDMP (99). However, limited evaluation of PDMPs at the state level has revealed mixed effects on changes in prescribing and mortality outcomes (20). 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.

Finally, regarding 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 of opioid overdose death at the community level (124).

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 (125), or interference with appropriate pain treatment (126). With the exception of a study noting an association between abuse-deterrent OxyContin formulation and heroin use, showing that some patients in qualitative interviews reported switching to another opioid including heroin (127), CDC did not identify studies evaluating these potential outcomes.

Provider and Patient Values and Preferences

Provider 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 (128), to predict (129) or detect (130) prescription drug abuse, and to discuss abuse with their patients (130). Although providers have reported favorable beliefs and attitudes about improvements in pain and quality of life attributed to opioids (131) 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%). Majorities have reported adverse events including tolerance (62%) and physical dependence (56%) occurring often among patients. Providers do not consistently use practices intended to decrease the risk of misuse, such as PDMPs (132, 133) urine drug testing (134), and opioid treatment agreements (135). 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 EHR systems) (136), 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 (137).

Many patients do not have an opinion about “opioids,” or know what this term means (138). Most are familiar with “narcotics.” About a third associated “narcotics” with addiction or abuse, and about half feared “addiction” from long-term “narcotic” use (138). Most patients taking opioids experience side effects (73% of patients taking hydrocodone for non-cancer pain (139), 96% of patients taking opioids for chronic pain (140)), and side effects, rather than pain relief, have been found to explain most of the variation in patients’ preferences related to taking opioids (140). For example, patients taking hydrocodone for non-cancer pain commonly reported side effects including dizziness, headache, fatigue, drowsiness, nausea, vomiting, and constipation (139). Chronic pain patients in focus groups emphasized effectiveness of goal setting for increasing motivation and functioning (141).

Patients taking high dosages report reliance on opioids despite ambivalence about their benefits (142) and regardless of pain reduction, report problems, concerns, side effects, or perceived helpfulness (143).

Resource Implications

Cost is an important consideration in understanding the feasibility of clinical recommendations. CDC searched for evidence on opioid therapy compared to alternative 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 non-medical use of prescription opioids (144), \$55.7 billion for abuse, dependence, and misuse of prescription opioids (145), and \$20.4 billion for direct and indirect costs related to opioid-related overdose alone (146). Although there are perceptions that opioid therapy for chronic pain is less expensive than more time-intensive non-pharmacologic 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 (147). COX-2 inhibitors, SNRIs, anticonvulsants, topical analgesics, physical therapy, and CBT are also associated with lower median annual costs compared with opioid therapy (10). 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 between \$211 and \$363 per test (148).

Recommendations

The recommendations are categorized into three areas for consideration:

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

There are 12 recommendations. Each recommendation is followed by a rationale for the recommendation, with considerations for implementation noted. In accordance with the GRADE process, CDC based the recommendations on consideration of the clinical evidence, contextual evidence (including benefits and harms, values and preferences, resource implications), and expert opinion. For each recommendation statement, CDC notes the strength of the recommendation (strong or weak) and the strength of the evidence (high, moderate, low, very low) supporting the statement. Experts from the Core Expert Group (“experts”) expressed 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.

Determining When to Initiate or Continue Opioids for Chronic Pain Outside of End-of-Life Care

- 1. Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Providers should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks** (strong recommendation, low quality of evidence).

Patients with pain should receive treatment that provides the greatest benefits relative to risks. Although opioids can reduce pain during short-term use, effects appear relatively small, and the clinical evidence review found insufficient evidence to determine whether pain relief is sustained or whether function or quality of life improves with long-term use of opioids (KQ1). While benefits in pain, function, and quality of life with long-term opioid use for chronic pain are uncertain, risks of 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 of abuse and dependence, overdose, myocardial infarction, and motor vehicle crashes (KQ2). At a population level, more than 16,000 persons in the United States die from opioid pain medication-related overdoses every year (contextual evidence review).

Based on contextual evidence, many non-pharmacologic therapies, including exercise therapy, weight loss, and psychological therapies such as CBT can ameliorate chronic pain. In particular, exercise therapy and CBT are activating therapies that address psychosocial contributors to pain and improve function. Several non-opioid 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, and antidepressants such as tricyclics and SNRIs as well as selected anticonvulsants are effective in neuropathic pain conditions and in fibromyalgia (contextual evidence review). Non-opioid pharmacologic therapies are associated with some risks, particularly in older patients, pregnant patients, and patients with certain co-morbidities such as cardiovascular, renal, and liver disease (contextual evidence review). However, these therapies are not associated with drug dependence, and the numbers of fatal overdoses associated with the non-opioid medications studied are a fraction of those associated with opioid medications (contextual evidence review).

Given uncertain benefits and substantial risks, experts agreed that opioids should not be considered first-line or routine therapy for chronic pain outside of end-of-life care. Non-pharmacologic therapy including exercise therapy and CBT should be used to reduce pain and improve function in patients with chronic pain. If pharmacologic therapy is needed, non-pharmacologic therapy should be used in combination with non-opioid pharmacologic therapy to reduce pain and improve function.

2. **Before starting long-term opioid therapy, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety** (strong recommendation, very low quality of evidence).

The clinical evidence review found insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and found an increased risk of 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 with inconsistent results (KQ4). These findings suggest it is very difficult for providers to predict whether benefits of opioids for chronic pain will outweigh risks of ongoing treatment for individual patients.

Experts agreed that before opioid therapy is initiated for chronic pain outside of end-of-life care, providers should determine how effectiveness will be evaluated and should establish treatment goals with patients. While the clinical evidence review did not find studies evaluating the effectiveness of written agreements or treatment plans (KQ4), providers 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, if opioids are no longer needed, or if adverse events put the patient at risk), to improve patient safety. Experts agreed that providers may use validated instruments such as the three-item “Pain average, interference with Enjoyment of life, and interference with General activity” (PEG) Assessment Scale (149) to track patient outcomes. Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function (150). Monitoring progress toward patient-centered functional goals (e.g., walking the dog or walking around the block, returning to part-time work, attending kids’ games) can also contribute to the assessment of functional improvement. If patients on long-term opioid therapy do not experience meaningful improvements in both pain and function compared with prior to initiation of opioid therapy, providers should consider working with patients to taper and discontinue opioids (see Recommendation 7) and should use non-pharmacologic and non-opioid pharmacologic approaches to pain management (see Recommendation 1).

3. Before starting and periodically during opioid therapy, providers should discuss with patients risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy (strong recommendation, low quality of evidence).

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 providers miss opportunities to effectively communicate about safety (e.g., when unexpected results are found in PDMP information or on urine drug testing). 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 is 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 provider and patient responsibilities to mitigate risks of opioid therapy.

Providers should involve patients in decisions about whether to start or continue opioid therapy. Given potentially serious risks of long-term opioid therapy, providers should ensure that patients are aware of potential benefits of, harms of, and alternatives to opioids before starting or continuing opioid therapy. Providers should:

- Be explicit and realistic about expected benefits of opioids, explaining that there is not 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 common adverse effects of opioids such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opioids as well as more serious adverse effects of opioids including development of a potentially serious lifelong opioid use disorder and potentially fatal overdose.
- Discuss increased risks for opioid use disorder, overdose, and death at higher dosages along with the importance of taking only the amount of opioids prescribed and not more opioids or more often.
- Review increased risks of overdose when opioids are taken with benzodiazepines, other sedatives, alcohol, illicit drugs such as heroin, or other opioids.
- Discuss the importance of periodic re-assessment to ensure that opioids are helping to meet patient goals and to allow opportunities for opioid discontinuation and consideration of alternative 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).
- Discuss risks to family members and individuals in the community if opioids are intentionally or unintentionally shared with others for whom they are not prescribed, including the possibility that others may experience overdose at the same or at lower dosage than prescribed for the patient. Discuss storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids (151).

Given the possibility that benefits of opioid therapy might diminish or that risks might become more prominent over time, it is important that providers 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, providers should prescribe short-acting opioids instead of extended-release/long-acting (ER/LA) opioids (strong recommendation, very low quality of evidence).**

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 of overdose among patients initiating treatment with ER/LA opioids than among those initiating treatment with short-acting opioids. The clinical evidence review did not find evidence that continuous, time-scheduled use of long acting opioids is more effective or safer than intermittent use of short-acting opioids or that time-scheduled use of long acting opioids reduces risks of opioid misuse or addiction (KQ3).

In 2013, the FDA modified the labeling for ER/LA opioid analgesics, 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.” 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 short-acting opioids for breakthrough pain when ER/LA opioids are used for chronic pain outside of end-of-life care, and that this practice might be associated with dose escalation.

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 of fatal overdose when methadone or transdermal fentanyl are prescribed to patients who have not used them previously or by providers who are not familiar with their effects.

Experts agreed that providers should not initiate opioid treatment with ER/LA opioids and should not prescribe ER/LA opioids for intermittent use. When opioids are used for chronic pain, as-needed, intermittent dosing with short-acting opioids might minimize total daily opioid dosage compared with continuous use of ER/LA opioids. ER/LA opioids should be reserved for severe, continuous pain. Providers should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or hepatic dysfunction, as decreased clearance of drugs in these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations. While there might be situations in which clinicians need to prescribe short-acting and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to short-acting opioids by temporarily using lower dosages of both), in general, it is preferable to avoid use of short-acting opioids in combination with ER/LA opioids for chronic pain outside of end-of-life care.

When an ER/LA opioid is used, it is preferable to use one with predictable pharmacokinetics and pharmacodynamics 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 providers who are familiar with methadone's unique risk profile and who are prepared to educate and closely monitor their patients, including risk assessment for QT prolongation and consideration of electrocardiographic monitoring, should consider prescribing methadone for pain.
- Because dosing effects of transdermal fentanyl are often misunderstood by both providers and patients, only providers who are familiar with the dosing and absorption properties of transdermal fentanyl and who are prepared to educate their patients about its use should consider prescribing it.

5. When opioids are started, providers should prescribe the lowest possible effective dosage. Providers should implement additional precautions when increasing dosage to ≥ 50 MME/day and should avoid increasing dosages to ≥ 90 MME/day (strong recommendation, low quality of evidence).

Benefits of high-dose opioids in chronic pain are not established. The clinical evidence review found only one study 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 increased opioid dosages are associated with increased risks of motor vehicle crashes, opioid abuse or dependence, and overdose (KQ2). The clinical and contextual evidence reviews found that opioid overdose risk increases in a dose-response manner at opioid dosages > 20 MME daily compared with dosages of 1 to 19 MME/day, and that dosages of 50 to 99 MME/day have been found to increase risks for opioid overdose by factors of 1.9 to 4.6 compared with dosages of 1 to 19 MME/day. Dosages ≥ 100 MME/day are associated with increased risks of overdose between 2.0 and 8.9 times the risk at 1 to 19 MME/day.

The contextual evidence review found that while there is not a single dosage threshold below which overdose risk is eliminated, holding dosages below 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 of overdose, but that a single dosage threshold for safe opioid use could not be identified. Experts noted that daily opioid dosages less than 50 MME/day are safer than dosages between 50 and 100 MME/day, and that dosages less than 20 MME/day are safer than dosages between 20 and 50 MME/day. 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. Experts agreed that additional precautions should be taken when patients are prescribed daily opioid dosages of ≥ 50 MME/day and that opioid dosages should generally not be increased to ≥ 90 MME/day.

When opioids are used for chronic pain outside of end-of-life care, providers should start opioids at the lowest possible effective dosage (i.e., the lowest starting dosage on product labeling). Providers should use additional caution when initiating opioids for patients ≥ 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. Providers should use caution when increasing opioid dosages, because overdose risk increases with increases in opioid dosage. If a patient's opioid dosage for all sources of opioids combined reaches or exceeds 50 MME/day, providers should reassess the patient's pain, function, and treatment, and should implement additional precautions, including increased frequency of follow-up (see Recommendation 7). Providers should take additional steps to mitigate overdose risk for patients receiving total daily opioid dosages of ≥ 50 MME/day, such as considering offering naloxone and overdose prevention education to both patients and the patient's household members (see Recommendation 8). Providers should avoid increasing opioid dosages to ≥ 90 MME/day. If patients do not experience improvement in pain and function at ≥ 90 MME/day, or if there are escalating dosage requirements, providers should discuss other approaches to pain management with the patient and should consider working with patients to taper and discontinue opioids (see Recommendation 7).

- 6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, providers should prescribe the lowest effective dose of short-acting opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three or fewer days will usually be sufficient for non-traumatic pain not related to major surgery (strong recommendation, very low quality of evidence).**

The clinical evidence review found that opioid use for acute pain is associated with long-term opioid use and that a greater amount of early opioid exposure is associated with greater risk of long-term use (KQ5). Several guidelines on opioid prescribing for acute pain have recommended prescribing ≤ 3 days of opioids in most cases (152-156). Given 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 should also 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 and also 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, providers 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. In most cases of acute pain not related to major surgery or trauma, three or fewer days' supply of opioids will be sufficient. Providers should consider a default of three or fewer days of opioids for acute pain, and adjust the duration based on the circumstances of the pain syndrome or surgical procedure. Providers should not prescribe additional opioids to patients "just in case" pain continues longer than expected. Providers should re-evaluate patients who experience 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 such as respiratory depression with ER/LA opioids, providers should not prescribe ER/LA opioids for the treatment of acute pain.

- 7. Providers should evaluate patients within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation to assess benefits and harms of continued opioid therapy. Providers should evaluate patients receiving long-term opioid therapy every 3 months or more frequently for benefits and harms of continued opioid therapy. If benefits do not outweigh harms of continued opioid therapy, providers should work with patients to reduce opioid dosage and to discontinue opioids when possible (strong recommendation, very low quality of evidence).**

While the clinical evidence review did not find studies evaluating the effectiveness of more frequent monitoring intervals (KQ4), it found that continuing opioid therapy for 3 months substantially increases risk of opioid use disorder (KQ2). In addition, risk of 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. While evidence is insufficient to determine at what point within the first 3 months of opioid therapy the risks for opioid use disorder increase, re-assessment 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 of opioid overdose are greatest during the first 3 to 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.

Providers 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. Providers 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 or greater. Shorter follow-up intervals (within 3 days) should be strongly considered when starting or increasing the dosage of methadone. At follow up, providers should assess benefits in function, pain, 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 (149) and/or asking patients about progress toward functional goals that have meaning for them (see Recommendation 2). Providers should also ask patients about common adverse effects such as constipation and drowsiness (see Recommendation 3) as well as effects that might be early warning signs for more serious problems such as overdose or opioid use disorder (e.g., sedation, wanting to take opioids in greater quantities or more frequently than prescribed). Because of potential changes in the balance of benefits and risks of opioid therapy over time, providers should regularly reassess at least every 3 months whether opioids continue to meet treatment goals including sustained improvement in pain and function, whether the patient has experienced common or serious adverse effects, whether benefits of opioids continue to outweigh risks, and whether opioid dosage can be reduced or opioids can be discontinued. Providers should re-evaluate patients who are exposed to greater risk (e.g., patients with depression or other mental health conditions, history of substance use disorder, taking ≥ 50 MME/day) more frequently than every 3 months. If clinically meaningful improvements in pain and function are not sustained, if patients are on high-risk regimens (e.g., dosages ≥ 50 MME/day or opioids combined with benzodiazepines) without evidence of benefit, if patients request dosage reduction or discontinuation, or if patients experience overdose or other serious adverse events (e.g., an event leading to hospitalization or disability), providers should work with patients to reduce opioid dosage and to discontinue opioids when possible.

Considerations for tapering opioids

While 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 dosage weekly by 10%-50% of the original dosage have been recommended by other clinical guidelines (157), and a rapid taper over 2-3 weeks has been recommended in the case of a severe adverse event such as overdose (23). Experts noted that tapers slower than 10% per week (e.g., 10% per month) might also 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, 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 need to be paused and restarted again when the patient is ready and might need 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., patients who have experienced overdose on their current dosage). Ultra-rapid detoxification under anesthesia is associated with substantial risks including death and should not be used (158). Providers should access appropriate expertise if considering tapering opioids during pregnancy. Patients who are not taking opioids (including patients who are diverting all opioids they obtain) do not require tapers. Providers should discuss with patients undergoing tapering the increased risk of overdose on abrupt return to a previously prescribed higher dose. Non-opioid pain management (see Recommendation 1) as well as psychosocial support for anxiety related to the taper should be optimized. The Washington State Agency Medical Directors’ Group (2015) Interagency Guideline on Prescribing Opioids for Pain, Appendix on Reducing or Discontinuing Chronic Opioid Analgesic Therapy, available at <http://www.agencymeddirectors.wa.gov/guidelines.asp> (23), and the review “Tapering long-term opioid therapy in chronic non-cancer pain: evidence and recommendations for everyday practice,”(159) available at [http://www.mayoclinicproceedings.org/article/S0025-6196\(15\)00303-1/pdf](http://www.mayoclinicproceedings.org/article/S0025-6196(15)00303-1/pdf), contain more detailed guidance on tapering, including management of withdrawal symptoms. If a patient exhibits signs of opioid use disorder (dependence, addiction), providers 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, providers should evaluate risk factors for opioid-related harms. Providers should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid-related harms are present** (strong recommendation, very low quality of evidence).

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.

Patients with sleep-disordered breathing

Risk factors for sleep-disordered breathing include sleep apnea, congestive heart failure, and obesity. Experts noted that careful monitoring and cautious dose titration should be used if opioids are used in patients with mild sleep-disordered breathing. Providers 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

Providers should avoid initiating opioid therapy in pregnant women whenever possible given that opioid therapy during pregnancy has been associated with stillbirth, poor fetal growth, pre-term delivery, neonatal abstinence syndrome, and birth defects (contextual evidence review). For pregnant women already on opioids, providers 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).

Patients with renal or hepatic insufficiency

Providers should use additional caution and increased monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency given 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

Given reduced renal function and medication clearance even in the absence of renal disease, patients aged ≥ 65 years may have increased susceptibility to accumulation of opioids and reduced 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 may interact with opioids (such as benzodiazepines). Providers should use additional caution and increased monitoring (see Recommendations 4, 5, and 7) to minimize risks of opioids prescribed for patients ≥ 65 years. Experts suggested that providers educate older adults receiving opioids to avoid risky medication-related behaviors such as obtaining controlled medications from multiple prescribers and saving unused medications over time. Providers should also implement interventions to mitigate common risks of opioid therapy in older adults, such as exercise and/or bowel regimens to mitigate constipation, risk assessment for falls, and patient monitoring for cognitive impairment.

Patients with mental health conditions

Experts noted that providers should use additional caution and increased monitoring (see Recommendation 7) to mitigate potentially increased risk of opioid use disorder among patients with mental health conditions (including depression, anxiety disorders, and post-traumatic stress disorder (PTSD)), as well as increased risk of drug overdose among patients with depression. 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 of overdose (see Recommendation 11). Providers should ensure that treatment for depression is optimized. 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, providers 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 risk for abuse or misuse (KQ4). Providers should always exercise caution when considering or prescribing opioids for any patient with chronic pain outside of end-of-life care and should not overestimate the ability of these tools to rule out risks from long-term opioid therapy.

Providers should ask patients about drug and alcohol use and 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/or overdose. Providers should also provide specific counseling on increased risks of 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), though 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 abuse and overdose than persons without these conditions. If providers consider opioid therapy for chronic pain outside of end-of-life care in 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 below) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed. Experts also noted the importance of communicating with patients' substance use disorder treatment providers if 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. The contextual evidence review did not find any studies on effectiveness of prescribing naloxone for overdose prevention in 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). Experts agreed that it is preferable not to initiate opioid treatment that places patients at increased risk for opioid-related harms. There were divergent opinions regarding how likely naloxone is to be useful to patients and the circumstances under which it should be offered. However, most experts agreed that providers should consider offering naloxone

when prescribing opioids to patients at increased risk of overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients taking benzodiazepines with opioids, patients at risk for returning to a high dose to which they are no longer tolerant (e.g., patients recently released from prison), and patients on higher dosages of opioids (≥ 50 MME). In addition, experts thought providers could consider offering naloxone when prescribing opioids to patients who live with persons with opioid use disorder. 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.

- 9. Providers should review the patient’s history of controlled substance prescriptions using state PDMP data to determine whether the patient is receiving excessive opioid dosages or dangerous combinations that put him/her at high risk for overdose. Providers should review PDMP data when starting opioid therapy and periodically during long-term opioid therapy, ranging from every prescription to every 3 months** (strong recommendation, very low quality of evidence).

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. PDMPs do not currently include information on prescriptions dispensed from Veterans’ Health Administration facilities and often do not include prescriptions dispensed in other states. Certain states require providers to review PDMP data prior to each opioid prescription written (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>). 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 (20), 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 is available to prescribers in the PDMP. 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 provider practices, which might adversely affect patient safety.

The contextual review found there is variation in state policies that affect timeliness of PDMP data (and therefore benefits of reviewing PDMP data) as well as time and workload for providers in accessing PDMP data. In some states where ability to delegate access to other members of the health care team is permitted, workload for prescribers can be reduced. These differences might result in a different balance of benefits to provider workload in different states. Experts agreed that PDMPs are useful tools that should be consulted when starting opioid therapy and periodically during long-term opioid therapy. There was disagreement on how frequently providers 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.

Providers should review PDMP data for opioids and other controlled medications patients have received from additional prescribers to determine whether a patient is receiving excessive total opioid dosages or dangerous combinations (e.g., opioids combined with benzodiazepines) that put him/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., provider and delegate access permitted). Such a practice 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), providers' ease of access in reviewing PDMP data is expected to improve. In addition, improved timeliness of PDMP data will improve the value of PDMP data in identifying patient risks.

If patients are found to have multiple controlled substance prescriptions written by different providers, there are several actions that can augment providers' abilities to improve patient safety:

- Providers should discuss information from the PDMP with their patient and confirm that the patient is aware of the additional prescriptions. Occasionally, PDMP information may be incorrect (e.g., if another person has used the patient's identity to obtain prescriptions). Providers should discuss safety concerns with patients found to be receiving medications that put them at increased risk for respiratory depression and overdose when combined with opioids (e.g., benzodiazepines).
- If patients are receiving benzodiazepines, providers should avoid whenever possible prescribing opioids if not yet started, and consider tapering opioids if already initiated (see Recommendations 11 and 7).
- Providers 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, providers should discuss their safety concerns with their patient, consider tapering to a safer dosage (see Recommendations 5, and 7), and consider offering naloxone (see Recommendation 8).
- Providers should discuss safety concerns with other providers who are prescribing controlled substances for their patient. Ideally providers should first discuss concerns with their patients and inform them that they plan to coordinate care with the patient's other prescribers to improve the patient's safety.
- Providers should consider the possibility of a substance use disorder and discuss concerns with their patient (see Recommendation 12).
- If providers suspect their patient might be sharing or selling opioids and not taking them, providers 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 providers should consider other possible reasons for this test result (see Recommendation 10).

Experts agreed that providers 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 life-saving information (e.g., risks of opioids, overdose prevention) and interventions (e.g., safer prescriptions, non-opioid pain treatment (see Recommendation 1), naloxone (see Recommendation 8), effective treatment for substance use disorder (see Recommendation 12)).

10. Providers should use urine drug testing before starting opioids for chronic pain and consider urine drug testing at least annually for all patients on long-term opioid therapy to assess for prescribed medications as well as other controlled substances and illicit drugs (weak recommendation, very low quality of evidence).

Concurrent use of opioid pain medications with other opioid pain medications, benzodiazepines, or heroin can increase patients' risk of overdose. Urine drug tests can provide information about drug use that is not reported by the patient. In addition, urine drug tests can assist providers in identifying patients who 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 sometimes 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 might de-stigmatize their use. Experts noted that in addition to direct costs of urine drug testing, provider time is needed to interpret, confirm, and communicate results.

Experts agreed that prior to starting opioids for chronic pain and periodically during opioid therapy, providers 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 non-prescribed opioids, benzodiazepines, and heroin. While experts agreed that providers 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 provider.

Providers 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, 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. The Washington State Agency Medical Directors’ Group (2015) Interagency Guideline on Prescribing Opioids for Pain, Appendix on Urine Drug Testing, available at <http://www.agencymeddirectors.wa.gov/guidelines.asp> (23) contains detailed guidance on interpretation of urine drug test results, including tests to order and expected results, drug detection time in urine, drug metabolism, and other considerations. Providers 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 tetrahydrocannabinol (THC). Before ordering urine drug testing, providers should have a plan for responding to unexpected results. Providers should explain to patients that urine drug testing is intended to improve their safety and should explain expected results (e.g., presence of prescribed medication and absence of drugs, including illicit drugs, not reported by the patient). Providers 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. Providers should discuss unexpected results with the local laboratory or toxicologist and with patients. If unexpected results are not explained, they should be verified with more specific confirmatory testing that uses gas or liquid chromatography/mass spectrometry.

Providers should use unexpected results to improve patient safety (e.g., change in pain management strategy (see Recommendation 1), tapering/discontinuation of opioids (see Recommendation 7), more frequent re-evaluation (see Recommendation 7), offering naloxone (see Recommendation 8), and/or referral for treatment for substance use disorder (see Recommendation 12), all as appropriate). Providers should not terminate patients from care based on a urine drug test result, as this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including obtaining opioids from alternative sources and missed opportunities to facilitate treatment for substance use disorder.

11. Providers should avoid prescribing of opioid pain medication and benzodiazepines concurrently whenever possible (strong recommendation, low quality of evidence).

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 of concurrent benzodiazepine use in large proportions of opioid-related overdose deaths in epidemiologic series, 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 (160). Experts agreed that providers should avoid prescribing opioids concurrently with benzodiazepines whenever possible. Providers should taper benzodiazepines gradually if discontinued because abrupt withdrawal can be associated with hallucinations, seizures, and in rare cases, death (contextual evidence review). A commonly used tapering schedule that has been used safely and with moderate success in both elderly and younger patients is a reduction of the benzodiazepine dose by 25% every one to two weeks (161, 162). CBT increases tapering success rates and might be particularly helpful for patients struggling with a benzodiazepine taper (161). Because of greater risks of benzodiazepine withdrawal relative to opioid withdrawal, when patients require tapering of benzodiazepines and/or opioids to reduce risk of fatal respiratory depression, it might be safer and more practical to taper opioids first (see Recommendation 7). Experts emphasized that providers should communicate with mental health professionals managing the patient in order to coordinate care. In addition, if benzodiazepines prescribed for anxiety are tapered or discontinued, evidence-based psychotherapies (e.g., CBT) and/or specific anti-depressants or other non-benzodiazepine medications approved for anxiety should be offered to patients.

12. Providers should offer or arrange evidence-based treatment (usually opioid agonist treatment in combination with behavioral therapies) for patients with opioid use disorder (strong recommendation, low quality of evidence).

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 (see <http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf>) (163).

The clinical evidence review found prevalence of opioid dependence in primary care settings among patients with chronic pain on opioid therapy to be between 3% and 26% (KQ2). Opioid agonist treatment with buprenorphine or methadone maintenance therapy in combination with behavioral therapies has been demonstrated to be more effective in preventing relapse among patients with opioid use disorder than detoxification without maintenance medication (164, 165). However, treatment need in a community is often not met by capacity to provide buprenorphine or methadone maintenance therapy (166). Oral or long-acting injectable formulations of naltrexone may also be used as medication-assisted treatment for opioid use disorder in non-pregnant adults, particularly for highly motivated persons (167, 168). Experts agreed that providers 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 providers suspect opioid use disorder based on patient concerns or behaviors or on findings in prescription drug monitoring program data (Recommendation 9) or on urine drug testing (Recommendation 10), they should discuss their concern with their patient and provide an opportunity for the patient to disclose related concerns or problems. Providers should assess for the presence of opioid use disorder using *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) criteria (see <http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf>) (163). Alternatively, providers 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, providers should offer or arrange for patients to receive evidence-based treatment (usually opioid agonist treatment with buprenorphine or methadone maintenance therapy in combination with behavioral therapies) for opioid use disorder. Providers should also consider offering naloxone 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 providers can offer to taper and discontinue opioids (see Recommendation 7). For patients who choose to but are unable to taper, providers may re-assess 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 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 a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) to prescribe buprenorphine for opioid use disorder. Information about qualifications and the process to obtain a waiver are available from SAMHSA (169). The American Society of Addiction Medicine National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use (170), available at <http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/national-practice-guideline.pdf?sfvrsn=22>, contains additional guidance on induction, use, and monitoring of buprenorphine treatment for opioid use disorder (see Part 5).

Providers unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a substance use disorder treatment specialist who can provide medication-assisted therapy such as an office-based buprenorphine treatment provider or an opioid treatment program. Providers should assist patients in finding qualified treatment providers and should arrange for patients to follow up with these providers and/or for ongoing coordination of care. Providers should not dismiss patients from their practice because of a substance use disorder as this can adversely affect patient safety and could represent patient abandonment. Identification of substance use disorder represents an opportunity for a provider to provide potentially life-saving interventions, and it is important for the provider to collaborate with the patient regarding their safety in order to increase the likelihood of successful treatment.

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

Future Directions

Clinical guidelines represent one strategy to improve 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 is dedicated to translating 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 providers, and engaging in dissemination efforts. Activities such as development of clinical decision support in electronic health records to assist providers' 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. Clinical guidelines complement other strategies aimed at preventing illnesses and injuries that lead to pain, 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 (171).

This guideline provides recommendations that are based on the best available evidence 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 in the National Pain Strategy (171) and also 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" (172). The NIH panel recommended that research is

needed to understand 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. Research that contributes to safer and more effective pain treatment can be implemented across public health entities and federal agencies (4). CDC will revisit this guideline as needed to determine if 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.

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SUMMARY RECOMMENDATIONS

Determining When to Initiate or Continue Opioids for Chronic Pain Outside of End-of-Life Care

1. Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Providers should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks (strong recommendation, low quality of evidence).
2. Before starting long-term opioid therapy, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (strong recommendation, very low quality of evidence).
3. Before starting and periodically during opioid therapy, providers should discuss with patients risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy (strong recommendation, low quality of evidence).

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

4. When starting opioid therapy, providers should prescribe short-acting opioids instead of extended-release/long-acting (ER/LA) opioids (strong recommendation, very low quality of evidence).
5. When opioids are started, providers should prescribe the lowest possible effective dosage. Providers should implement additional precautions when increasing dosage to ≥ 50 MME/day and should avoid increasing dosages to ≥ 90 MME/day (strong recommendation, low quality of evidence).
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, providers should prescribe the lowest effective dose of short-acting opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three or fewer days will usually be sufficient for non-traumatic pain not related to major surgery (strong recommendation, very low quality of evidence).
7. Providers should evaluate patients within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation to assess benefits and harms of continued opioid therapy. Providers should evaluate patients receiving long-term opioid therapy every 3 months or more frequently for benefits and harms of continued opioid therapy. If benefits do not outweigh harms of continued opioid therapy, providers should work with patients to reduce opioid dosage and to discontinue opioids when possible (strong recommendation, very low quality of evidence).

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, providers should evaluate risk factors for opioid-related harms. Providers should incorporate strategies into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid-related harms are present (strong recommendation, very low quality of evidence).
9. Providers should review the patient's history of controlled substance prescriptions using state PDMP data to determine whether the patient is receiving excessive opioid dosages or dangerous combinations that put him/her at high risk for overdose. Providers should review PDMP data when starting opioid therapy and periodically during long-term opioid therapy, ranging from every prescription to every 3 months (strong recommendation, very low quality of evidence).
10. Providers should use urine drug testing before starting opioids for chronic pain and consider urine drug testing at least annually for all patients on long-term opioid therapy to assess for prescribed medications as well as other controlled substances and illicit drugs (weak recommendation, very low quality of evidence).
11. Providers should avoid prescribing of opioid pain medication and benzodiazepines concurrently whenever possible (strong recommendation, low quality of evidence).
12. Providers should offer or arrange evidence-based treatment (usually opioid agonist treatment in combination with behavioral therapies) for patients with opioid use disorder (strong recommendation, low quality of evidence).

TABLE 1. GRADE Clinical Evidence Review Ratings

Outcome	Studies	Limitations	Inconsistency	Imprecision	Strength of evidence	Other factors	Estimates of effect/findings
Effectiveness and comparative effectiveness (KQ1)							
Effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (>1 year) outcomes							
Pain, function, and quality of life	None	–	–	–	Very low	–	No evidence
Harms and adverse events (KQ2)							
Risks of opioids versus placebo or no opioids on opioid abuse, addiction, and related outcomes; overdose; and other harms							
Abuse or addiction	1 cohort study (n = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	Low	–	One retrospective cohort study found prescribed long-term use of prescribed opioids associated with an increased risk of abuse or dependence diagnosis versus no opioid use (adjusted OR ranged from 14.9 to 122.5, depending on dose).
Abuse or addiction	10 uncontrolled studies (n = 3,780)	Very serious limitations	Very serious inconsistency	No imprecision	Very low	–	In primary care settings, prevalence of opioid abuse ranged from 0.6% to 8% and prevalence of dependence from 3% to 26%. In pain clinic settings, prevalence of misuse ranged from 8% to 16% and addiction from 2% to 14%. Prevalence of aberrant drug-related behaviors ranged from 6% to 37%.
Overdose	1 cohort study (n = 9,940)	Serious limitations	Unknown (1 study)	Serious imprecision	Low	–	Current opioid use associated with increased risk of any overdose events (adjusted HR 5.2, 95% CI = 2.1 - 12) and serious overdose events (adjusted HR 8.4, 95% CI = 2.5 - 28) versus current nonuse.

Fractures	1 cohort study ($n = 2,341$) and 1 case-control study ($n = 21,739$ case patients)	Serious limitations	No inconsistency	No imprecision	Low	–	Opioid use associated with increased risk of fracture in 1 cohort study (adjusted HR 1.28, 95% CI = 0.99 - 1.64) and 1 case-control study (adjusted OR 1.27, 95% CI = 1.21 - 1.33).
Myocardial infarction	1 cohort study ($n = 426,124$) and 1 case-control study ($n = 11,693$ case patients)	No limitations	No inconsistency	No imprecision	Low	–	Current opioid use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95% CI = 1.19 - 1.37 and incidence rate ratio 2.66, 95% CI = 2.30 - 3.08).
Endocrinologic harms	1 cross-sectional study ($n = 11,327$)	Serious limitations	Unknown (1 study)	No imprecision	Low	–	Long-term opioid use associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI = 1.1 - 1.9).

How do harms vary depending on the opioid dose used?

Abuse or addiction	1 cohort study (<i>n</i> = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	Low	–	One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared to no opioid prescription, the adjusted odds ratios were 15 (95 percent CI = 10 to 21) for 1 to 36 MME/day, 29 (95 % CI = 20 to 41) for 36 to 120 MME/day, and 122 (95 % CI = 73 - 205) for ≥120 MME/day.
Overdose	1 cohort study (<i>n</i> = 9,940) and 1 case–control study (<i>n</i> = 593 case patients in primary analysis)	Serious limitations	No inconsistency	No imprecision	Low	Magnitude of effect, dose response relationship	Versus 1 to 19 MME/day, 1 cohort study found an adjusted HR for an overdose event of 1.44 (95% CI = 0.57 - 3.62) for 20 to 49 MME/day that increased to 11.18 (95% CI = 4.80 - 26.03) at >100 MME/day; 1 case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI = 0.94 - 1.84) for 20 to 49 MME/day that increased to 2.88 (95% CI = 1.79 - 4.63) at ≥200 MME/day.

Fractures	1 cohort study (<i>n</i> = 2,341)	Serious limitations	Unknown (1 study)	Serious imprecision	Low	–	Risk of fracture increased from an adjusted HR of 1.20 (95% CI = 0.92 - 1.56) at 1 to <20 MME/day to 2.00 (95% CI = 1.24 - 3.24) at ≥50 MME/day; the trend was of borderline statistical significance.
Myocardial infarction	1 cohort study (<i>n</i> = 426,124)	Serious limitations	Unknown (1 study)	No imprecision	Low	–	Relative to a cumulative dose of 0 to 1350 MME over 90 days, the incidence rate ratio for myocardial infarction for 1350 to <2700 MME was 1.21 (95% CI = 1.02 - 1.45), for 2700 to <8100 MME was 1.42 (95% CI = 1.21 - 1.67), for 8100 to <18,000 MME was 1.89 (95% CI = 1.54 - 2.33), and for >18,000 MME was 1.73 (95% CI = 1.32 - 2.26).
Motor vehicle crash injuries	1 case-control study (<i>n</i> = 5,300 case patients)	No limitations	Unknown (1 study)	No imprecision	Low	–	No association between opioid dose and risk of motor vehicle crash injuries.

Endocrinologic harms	1 cross-sectional study (<i>n</i> = 11,327) New for update: 1 additional cross-sectional study (<i>n</i> =1,585)	Serious limitations	Consistent	No imprecision	Low	–	Relative to 0 to <20 MME/day, the adjusted OR for ≥120 MME/day for use of medications for erectile dysfunction or testosterone replacement was 1.6 (95% CI = 1.0 - 2.4). One new cross-sectional study found higher-dose long-term opioid therapy associated with increased risk of androgen deficiency among men receiving short-acting opioids (adjusted OR per 10 MME/day 1.16, 95% CI = 1.09 - 1.23), but the dose response was very weak among men receiving ER/LA opioids.
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Dosing strategies (KQ3)

Comparative effectiveness of different methods for initiating opioid therapy and titrating doses

Pain	3 randomized trials (<i>n</i> = 93)	Serious limitations	Serious inconsistency	Very serious imprecision	Very low	–	Trials on effects of titration with short-acting versus ER/LA opioids reported inconsistent results and had additional differences between treatment arms in dosing protocols (titrated versus fixed dosing) and doses of opioids used.
Overdose	New for update: 1 cohort study (<i>n</i> = 840,606)	Serious limitations	Unknown (1 study)	No imprecision	Very low	–	One new cross-sectional study found initiation of therapy with an ER/LA opioid associated with increased risk of overdose versus initiation with a short-acting opioid (adjusted HR 2.33, 95% CI = 1.26 - 4.32).

Comparative effectiveness of different ER/LA opioids

Pain and function	3 randomized trials (<i>n</i> = 1,850)	Serious limitations	No inconsistency	No imprecision	Low	–	No differences
All-cause mortality	1 cohort study (<i>n</i> = 108,492) New for update: 1 cohort study (<i>n</i> = 38,756)	Serious limitations	Serious inconsistency	No imprecision	Very low	–	One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity adjusted analysis (adjusted HR 0.56, 95% CI = 0.51 - 0.62) and one cohort study in Tennessee Medicaid patients found methadone to be associated with higher risk of all-cause mortality than sustained-release morphine (adjusted HR 1.46, 95% CI = 1.17 - 1.73).
Abuse and related outcomes	1 cohort study (<i>n</i> = 5,684)	Serious limitations	Unknown (1 study)	Serious imprecision	Very low	–	One cohort study found some differences between ER/LA opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions.
Long- versus short-acting opioids							
Endocrinologic harms	New for update: 1 cross-sectional study (<i>n</i> = 1,585)	Serious limitations	Unknown (1 study)	No imprecision	Very low	–	One cross-sectional study found ER/LA opioids associated with increased risk of androgen deficiency versus short-acting opioids (adjusted OR 3.39, 95% CI = 2.39 - 4.77).

Dose escalation versus dose maintenance or use of dose thresholds

Pain, function, or withdrawal due to opioid misuse	1 randomized trial (<i>n</i> = 140)	Serious limitations	Unknown (1 study)	Very serious imprecision	Low	–	No difference between more liberal dose escalation versus maintenance of current doses in pain, function, or risk of withdrawal due to opioid misuse, but there was limited separation in opioid doses between groups (52 versus 40 MME/day at the end of the trial).
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Short-acting versus ER/LA opioids; short-acting plus ER/LA opioids versus ER/LA opioids alone; scheduled and continuous versus as-needed dosing of opioids; or opioid rotation versus maintenance of current therapy

Pain, function, quality of life, and outcomes related to abuse	None	–	–	–	Very low	–	No evidence
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Effects of decreasing or tapering opioid doses versus continuation of opioid therapy

Pain and function	1 randomized trial (<i>n</i> = 10)	Very serious limitations	Unknown (1 study)	Very serious imprecision	Very low	–	Abrupt cessation of morphine was associated with increased pain and decreased function compared with continuation of morphine.
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Comparative effectiveness of different tapering protocols and strategies

Opioid abstinence	2 nonrandomized trials (<i>n</i> = 150)	Very serious limitations	No inconsistency	Very serious imprecision	Very low	–	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3 - 6 months
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Risk assessment and risk mitigation strategies (KQ4)

Diagnostic accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse in patients with chronic pain being considered for long-term opioid therapy

Opioid Risk Tool	3 studies of diagnostic accuracy (<i>n</i> = 496) New for update: 2 studies of diagnostic accuracy (<i>n</i> = 320)	Serious limitations	Very serious inconsistency	Serious imprecision	Very low	–	Based on a cutoff of >4 (or unspecified), five studies (two fair-quality, three poor-quality) reported sensitivity that ranged from 0.20 to 0.99 and specificity that ranged from 0.16 to 0.88).
Screener and Opioid Assessment for Patients with Pain, Version 1	2 studies of diagnostic accuracy (<i>n</i> = 203)	Very serious limitations	No inconsistency	Serious imprecision	Low	–	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity of 0.38 in 1 study, for a positive likelihood ratio of 1.11 and a negative likelihood ratio of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in 1 study.
Screener and Opioid Assessment for Patients with Pain- Revised	New for update: 2 studies of diagnostic accuracy (<i>n</i> = 320)	Very serious limitations	No inconsistency	Serious imprecision	Low	–	Based on a cutoff score of >3 or unspecified, sensitivity was 0.25 and 0.53 and specificity was 0.62 and 0.73 in 2 studies, for likelihood ratios close to 1.
Brief Risk Interview	New for update: 2 studies of diagnostic accuracy (<i>n</i> = 320)	Very serious limitations	No inconsistency	Serious imprecision	Low	–	Based on a “high risk” assessment, sensitivity was 0.73 and 0.83 and specificity was 0.43 and 0.88 in 2 studies, for positive likelihood ratios of 1.28 and 7.18 and negative likelihood ratios of 0.63 and 0.19.

Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain

Outcomes related to abuse	None	–	–	–	Very low	–	No evidence
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Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse

Outcomes related to abuse	None	–	–	–	Very low	–	No evidence
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Comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids

Outcomes related to abuse	None	–	–	–	Very low	–	No evidence
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Effects of opioid therapy for acute pain on long-term use (KQ5)

Long-term opioid use	New for update: 2 cohort studies (<i>n</i> = 399,852)	Serious limitations	No inconsistency	No imprecision	Low	–	One study found use of opioids within 7 days of low-risk surgery associated with increased likelihood of opioid use at 1 year (adjusted OR 1.44, 95% CI = 1.39 - 1.50) and one study found use of opioids within 15 days of onset of low back pain among workers with a compensation claim associated with increased risk of late opioid use (adjusted OR 2.08, 95% CI = 1.55 - 2.78 for 1-140 MME/day and OR 6.14, 95% CI = 4.92 - 7.66 for ≥450 MME/day).
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Abbreviations: OR = odds ratio, HR = hazard ratio, CI = confidence interval, MME = milligram morphine equivalents

Appendix A

Steering Committee and Core Expert Group Members

Steering Committee

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Appendix B**Core Expert Group (CEG) Disclosures**

The Core Expert Group (CEG) members wish to disclose they have no financial conflicts of interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. CDC reviewed content of disclosure statements to ensure there is no bias. CEG members wish to disclose the following activities related to the content of this guideline: Jayne Ballantyne wishes to disclose that she has served as a paid consultant to Cohen Milstein Sellers & Toll, PLLC and has special advisory committee responsibilities on the Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategies (REMS) committee; Phillip Coffin wishes to disclose that in 2012 he provided expert testimony to the California State Assembly regarding a bill to expand naloxone access and wishes to report that he is the principal investigator on a research study of methamphetamine dependence that receives donated Vivitrol (injectable naltrexone) from Alkermes Inc.; Erin Krebs wishes to disclose that she represented the American College of Physicians at a 2014 Food and Drug Administration meeting on Abuse Deterrent Opioid Formulations; Lewis Nelson wishes to disclose his ad-hoc membership on the FDA Drug Safety and Risk Management Advisory Committee; Robert “Chuck” Rich wishes to disclose that he was an author on the 2013 American Academy of Family Physicians position paper on opioids and pain management; Joanna Starrels wishes to disclose that she received honoraria from the Betty Ford Institute; Thomas Tape wishes to disclose that he was an author on the 2013 American College of Physicians policy position paper on prescription drug abuse.

Appendix C

Stakeholder Review Group

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



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CONTENTS

Introduction	1
Guideline Development Methods.....	4
Summary of the Clinical Evidence Review	8
Summary of the Contextual Evidence Review.....	11
Recommendations.....	16
Conclusions and Future Directions.....	33
References.....	35

Disclosure of Relationship

The Core Expert Group (CEG) members disclose that they have no financial conflicts of interest. Experts disclose the following activities related to the content of this guideline: Pam Archer discloses authorship of the Oklahoma Emergency Department and Urgent Care Clinic Opioid Prescribing Guidelines and the Opioid Prescribing Guidelines for Oklahoma Health Care Providers in the Office Based Setting; Bonnie Burman discloses authorship of the Ohio Guidelines for Prescribing Opioids for the Treatment of Chronic, Non-Terminal Pain; Jane Ballantyne discloses that she has served as a paid consultant to Cohen Milstein Sellers & Toll, PLLC, and has special advisory committee responsibilities on the Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategies committee; Phillip Coffin discloses that in 2012 he provided expert testimony to the California State Assembly regarding a bill to expand naloxone access and reports that he is the principal investigator on a research study of methamphetamine dependence that receives donated injectable naltrexone from Alkermes, Inc.; Gary Franklin discloses authorship of the AMDG Interagency Guideline on Prescribing Opioids for Pain; Erin Krebs discloses that she represented the American College of Physicians at a 2014 Food and Drug Administration meeting on Abuse Deterrent Opioid Formulations; Lewis Nelson discloses his ad-hoc membership on the FDA Drug Safety and Risk Management Advisory Committee; Trupti Patel discloses authorship of the Arizona Opioid Prescribing Guidelines; Robert “Chuck” Rich discloses that he was an author of the 2013 American Academy of Family Physicians position paper on opioids and pain management; Joanna Starrels discloses that she received honoraria from the Betty Ford Institute; Thomas Tape discloses that he was an author of the 2013 American College of Physicians policy

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The NCIPC Board of Scientific Counselors (BSC) members disclose that they have no financial conflicts of interest. Two BSC members, Traci Green and Christina Porucznik, served on the Opioid Guideline Workgroup. Traci Green discloses that she was previously employed by Inflexion, a small business that conducts Small Business Innovation Research on behavioral interventions for behavioral health and chronic pain and created several psychometric tools for conducting risk assessment for prescription opioid abuse potential. Dr. Green also discloses that while at the hospital where she is employed, she provided consultation to Purdue Pharma Ltd to design overdose prevention brochures for persons who use diverted prescription opioids non-medically with an emphasis on persons who inject prescription drugs, and not for patients using opioid therapy for pain. Dr. Green was recused from any discussion related to risk assessment tools and patient education materials. Christina Porucznik discloses that she served on the CDC Opioid Prescribing Guideline CEG.

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

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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>) as well as a website (<http://www.cdc.gov/drugoverdose/prescribingresources.html>) with additional tools to guide clinicians in implementing the recommendations.

Introduction

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

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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

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>). 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>). 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>). 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>).

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

* A list of the members appears at the end of this report. The recommendations and all statements included in this guideline are those of CDC and do not necessarily represent the official position of any persons or organizations providing comments on the draft guideline.

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>) 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>), 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

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>).

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>).

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>).

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

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>). 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>).

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>).

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>). 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

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.

BOX 1. CDC recommendations for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care**Determining When to Initiate or Continue Opioids for Chronic Pain**

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

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

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.

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

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

*All recommendations are category A (apply to all patients outside of active cancer treatment, palliative care, and end-of-life care) except recommendation 10 (designated category B, with individual decision making required); see full guideline for evidence ratings.

BOX 2. Interpretation of recommendation categories and evidence type**Recommendation Categories**

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

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

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

Evidence Type

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

Type 1 evidence: Randomized clinical trials or overwhelming evidence from observational studies.

Type 2 evidence: Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies.

Type 3 evidence: Observational studies or randomized clinical trials with notable limitations.

Type 4 evidence: Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.

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

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

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 trisilicate 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 \geq 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 \geq 50 MME/day. Most experts also agreed that opioid dosages should not be increased to \geq 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 \geq 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 \geq 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 \geq 90 MME/day or should carefully justify a decision to increase dosage to \geq 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 \geq 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 (\geq 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>.

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>). 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 tetrahydrocannabinol (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>) (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); SAMHSA's Opioid Treatment Program Directory (<http://dpt2.samhsa.gov/treatment/directory.aspx>); SAMHSA's Provider Clinical Support System for Opioid Therapies (<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>), which offers expert physician mentors to answer questions about assessment for and treatment of substance use disorders.

Conclusions and Future Directions

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>), additional resources such as fact sheets (<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.

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TABLE 1. Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical evidence review ratings of the evidence for the key clinical questions regarding effectiveness and risks of long-term opioid therapy for chronic pain

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of evidence	Other factors	Estimates of effect/findings
Effectiveness and comparative effectiveness (KQ1)							
Effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥1 year) outcomes							
Pain, function, and quality of life	None	—†	—	—	Insufficient	—	No evidence
Harms and adverse events (KQ2)							
Risks of opioids versus placebo or no opioids on opioid abuse, addiction, and related outcomes; overdose; and other harms							
Abuse or addiction	1 cohort study (n = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found long-term use of prescribed opioids associated with an increased risk of abuse or dependence diagnosis versus no opioid use (adjusted OR ranged from 14.9 to 122.5, depending on dose).
Abuse or addiction	10 uncontrolled studies (n = 3,780)	Very serious limitations	Very serious inconsistency	No imprecision	4	None identified	In primary care settings, prevalence of opioid abuse ranged from 0.6% to 8% and prevalence of dependence from 3% to 26%. In pain clinic settings, prevalence of misuse ranged from 8% to 16% and addiction from 2% to 14%. Prevalence of aberrant drug-related behaviors ranged from 6% to 37%.
Overdose	1 cohort study (n = 9,940)	Serious limitations	Unknown (1 study)	Serious imprecision	3	None identified	Current opioid use associated with increased risk of any overdose events (adjusted HR 5.2, 95% CI = 2.1–12) and serious overdose events (adjusted HR 8.4, 95% CI = 2.5–28) versus current nonuse.
Fractures	1 cohort study (n = 2,341) and 1 case-control study (n = 21,739 case patients)	Serious limitations	No inconsistency	No imprecision	3	None identified	Opioid use associated with increased risk of fracture in 1 cohort study (adjusted HR 1.28, 95% CI = 0.99–1.64) and 1 case-control study (adjusted OR 1.27, 95% CI = 1.21–1.33).
Myocardial infarction	1 cohort study (n = 426,124) and 1 case-control study (n = 11,693 case patients)	No limitations	No inconsistency	No imprecision	3	None identified	Current opioid use associated with increased risk of myocardial infarction versus nonuse (adjusted HR 1.28, 95% CI = 1.19–1.37 and incidence rate ratio 2.66, 95% CI = 2.30–3.08).
Endocrinologic harms	1 cross-sectional study (n = 11,327)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI = 1.1–1.9).
How do harms vary depending on the opioid dose used?							
Abuse or addiction	1 cohort study (n = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared to no opioid prescription, the adjusted odds ratios were 15 (95% CI = 10–21) for 1 to 36 MME/day, 29 (95% CI = 20–41) for 36 to 120 MME/day, and 122 (95% CI = 73–205) for ≥120 MME/day.
Overdose	1 cohort study (n = 9,940) and 1 case-control study (n = 593 case patients in primary analysis)	Serious limitations	No inconsistency	No imprecision	3	Magnitude of effect, dose response relationship	Versus 1 to <20 MME/day, one cohort study found an adjusted HR for an overdose event of 1.44 (95% CI = 0.57–3.62) for 20 to <50 MME/day that increased to 8.87 (95% CI = 3.99–19.72) at ≥100 MME/day; one case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI = 0.94–1.84) for 20 to 49 MME/day that increased to 2.88 (95% CI = 1.79–4.63) at ≥200 MME/day.
Fractures	1 cohort study (n = 2,341)	Serious limitations	Unknown (1 study)	Serious imprecision	3	None identified	Risk of fracture increased from an adjusted HR of 1.20 (95% CI = 0.92–1.56) at 1 to <20 MME/day to 2.00 (95% CI = 1.24–3.24) at ≥50 MME/day; the trend was of borderline statistical significance.

See table footnotes on page 47.

TABLE 1. (Continued) Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical evidence review ratings of the evidence for the key clinical questions regarding effectiveness and risks of long-term opioid therapy for chronic pain

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of evidence	Other factors	Estimates of effect/findings
Myocardial infarction	1 cohort study (n = 426,124)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Relative to a cumulative dose of 0 to 1,350 MME during a 90-day period, the incidence rate ratio for myocardial infarction for 1350 to <2700 MME was 1.21 (95% CI = 1.02–1.45), for 2,700 to <8,100 MME was 1.42 (95% CI = 1.21–1.67), for 8,100 to <18,000 MME was 1.89 (95% CI = 1.54–2.33), and for ≥18,000 MME was 1.73 (95% CI = 1.32–2.26).
Motor vehicle crash injuries	1 case–control study (n = 5,300 case patients)	No limitations	Unknown (1 study)	No imprecision	3	None identified	No association between opioid dose and risk of motor vehicle crash injuries even though opioid doses >20 MME/day were associated with increased odds of road trauma among drivers.
Endocrinologic harms	1 cross-sectional study (n = 11,327) New for update: 1 additional cross-sectional study (n=1,585)	Serious limitations	Consistent	No imprecision	3	None identified	Relative to 0 to <20 MME/day, the adjusted OR for ≥120 MME/day for use of medications for erectile dysfunction or testosterone replacement was 1.6 (95% CI = 1.0–2.4). One new cross-sectional study found higher-dose long-term opioid therapy associated with increased risk of androgen deficiency among men receiving immediate-release opioids (adjusted OR per 10 MME/day 1.16, 95% CI = 1.09–1.23), but the dose response was very weak among men receiving ER/LA opioids.
Dosing strategies (KQ3)							
Comparative effectiveness of different methods for initiating opioid therapy and titrating doses							
Pain	3 randomized trials (n = 93)	Serious limitations	Serious inconsistency	Very serious imprecision	4	None identified	Trials on effects of titration with immediate-release versus ER/LA opioids reported inconsistent results and had additional differences between treatment arms in dosing protocols (titrated versus fixed dosing) and doses of opioids used.
Overdose	New for update: 1 cohort study (n = 840,606)	Serious limitations	Unknown (1 study)	No imprecision	4	None identified	One new cross-sectional study found initiation of therapy with an ER/LA opioid associated with increased risk of overdose versus initiation with an immediate-release opioid (adjusted HR 2.33, 95% CI = 1.26–4.32).
Comparative effectiveness of different ER/LA opioids							
Pain and function	3 randomized trials (n = 1,850)	Serious limitations	No inconsistency	No imprecision	3	None identified	No differences
All-cause mortality	1 cohort study (n = 108,492) New for update: 1 cohort study (n = 38,756)	Serious limitations	Serious inconsistency	No imprecision	4	None identified	One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity-adjusted analysis (adjusted HR 0.56, 95% CI = 0.51–0.62) and one cohort study among Tennessee Medicaid patients found methadone to be associated with higher risk of all-cause mortality than sustained-release morphine (adjusted HR 1.46, 95% CI = 1.17–1.73).
Abuse and related outcomes	1 cohort study (n = 5,684)	Serious limitations	Unknown (1 study)	Serious imprecision	4	None identified	One cohort study found some differences between ER/LA opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions.
ER/LA versus immediate-release opioids							
Endocrinologic harms	New for update: 1 cross-sectional study (n = 1,585)	Serious limitations	Unknown (1 study)	No imprecision	4	None identified	One cross-sectional study found ER/LA opioids associated with increased risk of androgen deficiency versus immediate-release opioids (adjusted OR 3.39, 95% CI = 2.39–4.77).

See table footnotes on page 47.

TABLE 1. (Continued) Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical evidence review ratings of the evidence for the key clinical questions regarding effectiveness and risks of long-term opioid therapy for chronic pain

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of evidence	Other factors	Estimates of effect/findings
Dose escalation versus dose maintenance or use of dose thresholds							
Pain, function, or withdrawal due to opioid misuse	1 randomized trial (n = 140)	Serious limitations	Unknown (1 study)	Very serious imprecision	3	None identified	No difference between more liberal dose escalation versus maintenance of current doses in pain, function, or risk of withdrawal due to opioid misuse, but there was limited separation in opioid doses between groups (52 versus 40 MME/day at the end of the trial).
Immediate-release versus ER/LA opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled and continuous versus as-needed dosing of opioids; or opioid rotation versus maintenance of current therapy							
Pain, function, quality of life, and outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effects of decreasing or tapering opioid doses versus continuation of opioid therapy							
Pain and function	1 randomized trial (n = 10)	Very serious limitations	Unknown (1 study)	Very serious imprecision	4	None identified	Abrupt cessation of morphine was associated with increased pain and decreased function compared with continuation of morphine.
Comparative effectiveness of different tapering protocols and strategies							
Opioid abstinence	2 nonrandomized trials (n = 150)	Very serious limitations	No inconsistency	Very serious imprecision	4	None identified	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3–6 months
Risk assessment and risk mitigation strategies (KQ4)							
Diagnostic accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse among patients with chronic pain being considered for long-term opioid therapy							
Opioid risk tool	3 studies of diagnostic accuracy (n = 496) New for update: 2 studies of diagnostic accuracy (n = 320)	Serious limitations	Very serious inconsistency	Serious imprecision	4	None identified	Based on a cutoff score of >4 (or unspecified), five studies (two fair-quality, three poor-quality) reported sensitivity that ranged from 0.20 to 0.99 and specificity that ranged from 0.16 to 0.88.
Screeener and Opioid Assessment for Patients with Pain, Version 1	2 studies of diagnostic accuracy (n = 203)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity was 0.38 in one study, for a positive likelihood ratio of 1.11 and a negative likelihood ratio of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in one study.
Screeener and Opioid Assessment for Patients with Pain-Revised	New for update: 2 studies of diagnostic accuracy (n = 320)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a cutoff score of >3 or unspecified, sensitivity was 0.25 and 0.53 and specificity was 0.62 and 0.73 in two studies, for likelihood ratios close to 1.
Brief Risk Interview	New for update: 2 studies of diagnostic accuracy (n = 320)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a “high risk” assessment, sensitivity was 0.73 and 0.83 and specificity was 0.43 and 0.88 in two studies, for positive likelihood ratios of 1.28 and 7.18 and negative likelihood ratios of 0.63 and 0.19.

See table footnotes on page 47.

TABLE 1. (Continued) Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical evidence review ratings of the evidence for the key clinical questions regarding effectiveness and risks of long-term opioid therapy for chronic pain

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of evidence	Other factors	Estimates of effect/findings
Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effects of opioid therapy for acute pain on long-term use (KQ5)							
Long-term opioid use	New for update: 2 cohort studies (n = 399,852)	Serious limitations	No inconsistency	No imprecision	3	None identified	One study found use of opioids within 7 days of low-risk surgery associated with increased likelihood of opioid use at 1 year (adjusted OR 1.44, 95% CI = 1.39–1.50), and one study found use of opioids within 15 days of onset of low back pain among workers with a compensation claim associated with increased risk of late opioid use (adjusted OR 2.08, 95% CI = 1.55–2.78 for 1 to 140 MME/day and OR 6.14, 95% CI = 4.92–7.66 for ≥450 MME/day).

Abbreviations: CI = confidence interval; ER/LA = extended release/long-acting; HR = hazard ratio; MME = morphine milligram equivalents; OR = odds ratio.

* Ratings were made per GRADE quality assessment criteria; "no limitations" indicates that limitations assessed through the GRADE method were not identified.

† Not applicable as no evidence was available for rating.

TABLE 2. Morphine milligram equivalent (MME) doses for commonly prescribed opioids

Opioid	Conversion factor*
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1–20 mg/day	4
21–40 mg/day	8
41–60 mg/day	10
≥61–80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Tapentadol†	0.4

Source: Adapted from Von Korff M, Saunders K, Ray GT, et al. Clin J Pain 2008;24:521–7 and Washington State Interagency Guideline on Prescribing Opioids for Pain (<http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf>).

* Multiply the dose for each opioid by the conversion factor to determine the dose in MMEs. For example, tablets containing hydrocodone 5 mg and acetaminophen 300 mg taken four times a day would contain a total of 20 mg of hydrocodone daily, equivalent to 20 MME daily; extended-release tablets containing oxycodone 10mg and taken twice a day would contain a total of 20mg of oxycodone daily, equivalent to 30 MME daily. The following cautions should be noted: 1) All doses are in mg/day except for fentanyl, which is mcg/hr. 2) Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics. 3) Do not use the calculated dose in MMEs to determine the doses to use when converting opioid to another; when converting opioids the new opioid is typically dosed at substantially lower than the calculated MME dose to avoid accidental overdose due to incomplete cross-tolerance and individual variability in opioid pharmacokinetics. 4) Use particular caution with methadone dose conversions because the conversion factor increases at higher doses. 5) Use particular caution with fentanyl since it is dosed in mcg/hr instead of mg/day, and its absorption is affected by heat and other factors.

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

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National Pain Strategy

A Comprehensive Population Health-Level Strategy for Pain

Contents

EXECUTIVE SUMMARY.....	2
Population Research.....	3
Prevention and Care.....	3
Disparities	4
Service Delivery and Reimbursement.....	4
Professional Education and Training	4
Public Education and Communication.....	4
THE NATIONAL PAIN STRATEGY: A Vision	5
BACKGROUND TO THE PROJECT	6
INTRODUCTION	10
Population Research.....	14
Prevention and Care.....	20
Disparities	26
Service Delivery and Reimbursement.....	30
Professional Education and Training	36
Public Education and Communication.....	40
APPENDIXES	44
Appendix A. List of Oversight Panel Members.....	45
Appendix B. List of work group members, expert consultants, and staff.....	47
Appendix C. Member nomination process and conflict of interest disclosure	57
Appendix D. Chronic pain screener questions.....	58
Appendix E. Operational questions for determining high-impact chronic pain.....	59
Appendix F. Diagnostic clusters for population pain research	60
Appendix G. Pain treatment indicators: Health care services for pain measurable with electronic health care data	61
Appendix H. Public and private payer coverage and reimbursement methodologies for pain-related treatments	63
Appendix I. The VA Stepped Care Model of pain care	68
Appendix J. Core competencies for pain education.....	69
Appendix K. Public education general campaign learning objectives.....	70
Appendix L. Learning objectives and potential outcome measures for an educational campaign on safe use of pain medications	71

EXECUTIVE SUMMARY

In 2010, in response to a congressional mandate, the National Institutes of Health (NIH) contracted with the Institute of Medicine (IOM) to undertake a study and make recommendations “to increase the recognition of pain as a significant public health problem in the United States.” The Institute’s 2011 report called for a cultural transformation in pain prevention, care, education, and research and recommended development of “a comprehensive population health-level strategy” to address these issues. The Assistant Secretary for Health and Human Services (HHS) asked the Interagency Pain Research Coordinating Committee (IPRCC) to oversee creation of this resultant National Pain Strategy. Guided and coordinated by an oversight panel, expert working groups explored six important areas of need identified in the IOM recommendations—population research, prevention and care, disparities, service delivery and reimbursement, professional education and training, and public awareness and communication. The working groups comprised people from a broad array of relevant public and private organizations, including health care providers, insurers, and people with pain and their advocates.

As articulated in the IOM report, however, this cultural transformation in our efforts to reduce the burden of pain in the United States will not be achieved without sustained and indeed expanded investment into basic and clinical research studies of the biopsychosocial mechanisms that produce and maintain chronic pain and into the development of safe and effective pain treatments. As a first step in this critical direction the IPRCC has completed a comprehensive analysis of the existing federal pain research portfolio. The next steps will identify gaps in our understanding as well as directions for new research, which will guide the NIH and other federal agencies and departments in their support of these essential pain research programs.

Fundamental conclusions and implications drawn from the IOM report guided development of the National Pain Strategy, including:

- The public at large and people with pain, in particular, would benefit from a better understanding of pain and its treatment, in order to encourage timely care, improve medical management, and combat stigma.
- Increased scientific knowledge regarding the pathophysiology of pain has led to the conclusion that chronic pain can be a disease in itself that requires adequate treatment and a research commitment.
- Although pain is widespread in the population, data are lacking on the prevalence, onset, course, impact, and outcomes of most common chronic pain conditions. The greatest individual and societal benefit nevertheless would accrue from a focus on chronic pain.
- Every effort should be made to prevent illnesses and injuries that lead to pain, the progression of acute pain to a chronic condition, and the development of high-impact chronic pain.
- Significant improvements are needed in pain assessment techniques and practices to assure they are high-quality and comprehensive.
- Self-management programs can improve quality of life and is an important component of acute and chronic pain prevention and management.

- Chronic pain is a biopsychosocial condition that often requires integrated, multimodal, and interdisciplinary treatment, all components of which should be evidence-based.
- People with chronic pain need greater access to treatments that take into account their preferences and are in accord with best evidence on safety and effectiveness.
- New treatment approaches need to be developed that take into account individual differences that affect the onset of pain and response to treatment.
- Treatments that are ineffective, whose risks greatly exceed their benefits, or that may cause harm for certain subgroups need to be identified and their use curtailed or discontinued.
- Much of the responsibility for front-line pain care rests on primary care clinicians, who are not sufficiently trained in pain assessment and comprehensive, evidence-based treatment approaches.
- Greater collaboration is needed between primary care clinicians and pain specialists in different clinical disciplines and settings, including multispecialty pain clinics.
- Significant barriers to pain care exist, especially for populations disproportionately affected by and undertreated for pain, and need to be overcome.
- People with pain are too often stigmatized in the health care system and in society, which can lead to delayed diagnosis or misdiagnosis, bias in treatment, and decreased effectiveness of care.

The aforementioned expert working groups produced interrelated sets of objectives and suggested action plans in the six areas summarized below: population research, prevention and care, disparities, service delivery and reimbursement, professional education and training, and public education and communication.

Population Research

Understanding the significance of health problems in a population is a core public health responsibility. To increase the quantity and quality of what is known about chronic pain in the U.S. population, the National Pain Strategy recommends specific steps to a) increase the precision of information about chronic pain prevalence overall, for specific types of pain, and in specific population groups; b) develop the capacity to gather information electronically about pain treatments, their usage, costs, effectiveness, and safety; and c) enable tracking changes in pain prevalence, impact, and treatment over time, allowing evaluation of population-level interventions and identification of emerging needs.

Prevention and Care

Prevention of acute and chronic pain needs greater emphasis throughout the health care system, in environments where injuries are likely to occur, and for people at increased risk of developing chronic pain. When chronic pain develops, treatment should begin with a comprehensive assessment, followed by creation of a care plan that can evolve over time to address the full range of biological, psychological, and social effects of pain on the individual. That said, the National Pain Strategy recommends strengthening the evidence base for

pain prevention strategies, assessment tools, and outcome measures—particularly those relevant for primary care—in part through the development of new, rigorously researched approaches. It also recommends improvements in pain self-management programs that can help affected individuals improve their knowledge, skills, and confidence to prevent, reduce, and cope with pain.

Disparities

Pain is more prevalent in a diverse set of population groups typically of interest to public health programs, including people with limited access to health care services, racial and ethnic minorities, people with low income or education, and those at increased risk because of where they live or work. These groups often face the additional problem of stigma and bias in pain care. To eliminate disparities and promote equity in pain assessment and treatment, the NPS recommends efforts that would increase understanding of the impact of bias and would support effective strategies to overcome it; an increase in access to high-quality pain care for vulnerable population groups; and improvements in communication among patients and health professionals.

Service Delivery and Reimbursement

Evidence suggests that wide variations in clinical practices, inadequate tailoring of pain therapies to individuals, and reliance on relatively ineffective and potentially high risk treatments not only contribute to poor quality care for people with pain, but also increase health care costs. The National Pain Strategy endorses a population-based, biopsychosocial approach to pain care that is grounded in scientific evidence, integrated, multimodal, and interdisciplinary while, at the patient level is tailored to individual needs. Research and demonstration efforts are needed that build on current knowledge, develop new knowledge, and support further testing and diffusion of model delivery systems.

Professional Education and Training

Although pain is one of the most common reasons for health care visits, most health profession's education programs have yet to give it adequate attention. Improvements are needed in discipline-specific core competencies, including basic knowledge, assessment, effective team-based care, empathy, and cultural competency. Educational program accreditation bodies and professional licensure boards can require pain teaching and clinician learning at the undergraduate and graduate levels. The National Pain Strategy also recommends development of a web-based pain education portal that would contain up-to-date, comprehensive, and easily accessed educational materials.

Public Education and Communication

Key to a cultural transformation in pain care is a greater understanding—among members of the public and people with pain alike—of important aspects of chronic pain. The National Pain Strategy recommends a national public awareness campaign involving many relevant public and private partners, including people with pain and their advocates, to address stigma and misperceptions about chronic pain. The learning objectives the campaign would work to achieve would emphasize the impact and seriousness of chronic pain and its status as a disease in its own right that requires appropriate treatment. In addition, a safe-use education campaign targeting people with pain whose care includes prescription medications is recommended.

THE NATIONAL PAIN STRATEGY: A Vision

If the objectives of the National Pain Strategy are achieved, the nation would see a decrease in prevalence across the continuum of pain, from acute, to chronic, to high-impact chronic pain, and across the life span from pediatric through geriatric populations, to end of life, which would reduce the burden of pain for individuals, families, and society as a whole. Americans experiencing pain—across this broad continuum — would have timely access to a care system that meets their biopsychosocial needs and takes into account individual preferences, risks, and social contexts. In other words, they would receive patient-centered care.

Further, Americans in general would recognize chronic pain as a complex disease and a threat to public health and to a just and productive society. Because of this greater understanding, significant public resources would be invested in the areas of *preventing* pain, creating *access* to evidence-based and high-quality pain assessment and treatment services and improving *self-management* abilities among those with pain. In addition, individuals who live with chronic pain would be viewed and treated with *compassion and respect*. Specifically, substantial progress in the care system would be achieved as follows:

- Clinicians would take active prevention measures to prevent the progression of acute to chronic pain and its associated disabilities.
- Clinicians would undertake comprehensive assessments of patients with chronic pain, leading to an integrated plan of coordinated care, managed by an interdisciplinary team, when needed. Treatment would involve high-quality, state-of-the-art, multimodal, evidence-based practices. While most pain care would be coordinated by primary care practitioners, specialists would be involved judiciously in the care of patients who have increased co-morbidities, complexity, or risk.
- People with all levels of pain would have access to educational materials and effective approaches for self-care and pain self-management programs that would help them prevent, cope with, and reduce pain and its disability, and they would have better information about the benefits and risks of pain management options. The information would be available to those who have low literacy or communication disabilities.
- All Americans would be assured of obtaining preventive, assessment, treatment, and self-care interventions and support, regardless of age, gender, sex, race, ethnicity, income, education,

geographic location, language proficiency, health literacy, or medical condition. All pain-related services would be provided without bias, discrimination, or stigma.

Specific advances supporting the evolution toward a public health approach to pain prevention and care would result from improvements in clinical education, public and institutional policies and population-level epidemiologic, health services, social science, medical informatics, implementation, basic and translational biomedical, and other relevant research, informed by clinician/scientist interactions.

Primary care clinicians and specialists in relevant fields need to know more about the biopsychosocial characteristics and safe and appropriate management of pain. Clinicians' knowledge of pain and pain care would be broadened to encompass an understanding of individual variability in pain susceptibility and treatment effectiveness, how pain affects communication, the importance of shared and informed decision-making, ways to encourage pain self-management under mutually agreed-upon treatment plans, how clinician empathy and cultural sensitivity influences the effectiveness of care, and the role of complementary and integrative medicine.

Chief among the supporting policy approaches would be reimbursement incentives and payment structures that support population-based care models of proven effectiveness, especially in interdisciplinary settings, and encourage multimodal care geared toward improving a full range of patient outcomes.

Timely data regarding the health and economic burdens of chronic pain would guide federal and state governments and diverse health care organizations in their efforts to work toward these objectives. Such data would lay the groundwork for enhancing the effectiveness and safety of pain care overall and for specific population groups and would enable monitoring the effectiveness of policy initiatives, public education efforts, and changing treatment patterns.

Finally, electronic data on pain assessment and treatment would be standardized, and health systems would maintain pain data registries that include information on the psychosocial/functional impact of chronic pain and the costs and effectiveness of pain management interventions. These data resources would be used in an ongoing effort to evaluate, compare, and enhance health care systems, identify areas for further research, and assess therapies for quality and value.

BACKGROUND TO THE PROJECT

The 2010 Patient Protection and Affordable Care Act (ACA), Section 4305, required the Secretary of HHS to enter into an agreement with the IOM for activities “to increase the recognition of pain as a significant

public health problem in the United States.” As a result, HHS, working through the NIH, commissioned an IOM study to assess the state of pain care. The resultant IOM report, issued in June 2011,¹ included 16 recommendations for improvements in:

- data collection and reporting
- the availability and effectiveness of pain care
- public, patient, and professional education about pain, and
- related preclinical, translational, and clinical research.

The IOM’s emphasis on pain as a significant public health challenge, amenable to population health-level interventions, placed a large share of responsibility for implementing these recommendations on federal health agencies (Institute of Medicine, 2011, p. 5). Specifically, Recommendation 2-2 called for creation of “a comprehensive population health-level strategy for pain prevention, treatment, management, and research.”

The following year, in response to a congressional mandate, HHS created the federal IPRCC² to coordinate all pain research efforts within HHS and across other Federal Agencies and in October 2012, the Assistant Secretary for Health asked the IPRCC to oversee the creation of the comprehensive population health-level strategy envisioned in IOM Recommendation 2-2. The IPRCC and the NIH, under the leadership of Story Landis, Director, National Institute of Neurological Disorders and Stroke, established a framework for developing a National Pain Strategy and engaging the necessary expertise, in consultation with the Chair and Vice Chair of the IOM Committee.³

Six key areas addressed in the National Pain Strategy are:

- population research
- prevention and care
- disparities
- service delivery and reimbursement
- professional education and training, and
- public education and communication

¹ Institute of Medicine. 2011. *Relieving pain in America: A blueprint for transforming prevention, care, education, and research*. Washington, D.C.: National Academies Press.

² A list of the federal agency, scientific, public, and ex-officio members of the IPRCC can be found at <http://iprcc.nih.gov/committee/committee-roster.htm>.

³ Philip Pizzo, MD, former dean, Stanford University School of Medicine; Noreen Clark, PhD, Director, Center for Managing Chronic Disease, University of Michigan (deceased).

The IPRCC selected expert working groups to address each of these areas and created an oversight panel to guide and coordinate the working groups' interrelated efforts (Appendixes A and B). Nominations for working group and oversight panel membership were actively solicited from professional societies, federal and state agencies, private foundations, advocacy organizations, and through the Federal Register (Appendix C). The goal was broad representation from relevant public and private organizations, health care providers, insurers, and people with pain and their advocates, as recommended by the IOM committee. The results of the focused deliberation of these six work groups form the body of this report, which includes objectives and steps to achieving them in the short-, medium-, and longer-term, identifies stakeholders to implement the objectives, and suggests metrics for assessing progress. The report is intended to initiate a longer-term effort to create a cultural transformation in how pain is perceived, assessed, and treated—a significant step towards the ideal state of pain care. An ensuing strategy to address the contribution of research to this strategy will be developed by the IPRCC. Box 1 contains definitions.

Box 1

Definitions Used in This Report

Acute pain – An expected physiologic experience to noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviors to avoid actual or potential tissue injuries.

Biopsychosocial – A medical problem or intervention that combines biological, psychological, and social elements or aspects.

Chronic pain - Pain that occurs on at least half the days for six months or more.

Continuum of pain – The characterization of pain as a temporal process, beginning with an acute stage, which may progress to a chronic state of variable duration.

Disease management refers to a system of integrated, multidisciplinary interventions and communications for populations with chronic disorders in which self-care efforts are significant.

Disparities – The Disparities work group used the working definition created by Healthy People 2020, terming disparities “a particular type of health difference that is closely linked with social, economic, and/or

environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion.”⁴

High-impact chronic pain is associated with substantial restriction of participation in work, social, and self-care activities for six months or more.

Integrated care is the systematic coordination of medical, psychological and social aspects of health care and includes primary care, mental health care, and, when needed, specialist services.

Interdisciplinary care is provided by a team of health professionals from diverse fields who coordinate their skills and resources to meet patient goals.

Levels of care – *Primary care* practitioners provide routine screenings and assessment and management of common pain conditions due to headache, diabetes, arthritis, and low back pain, for example; *pain medicine specialists* provide secondary-level consultations, which can include multidisciplinary team-based care, including rehabilitation therapy and behavioral health care; *interdisciplinary pain centers* provide tertiary care through advanced pain medicine diagnostics and interventions.

Multimodal pain treatment addresses the full range of an individual patient’s biopsychosocial challenges by providing a range of multiple and different types of therapies as needed.

Pain self-management programs address the systematic provision of education and supportive interventions by health care providers to strengthen patients’ skills and confidence in medical management, role management, and emotional management of their health problems, including regular assessment of progress and problems, decision making, goal setting, self-monitoring, and problem solving. Specifically for pain self-management, these programs involve acquiring knowledge about pain and building skills and confidence to prevent, cope with, and reduce pain. These programs can stand alone and be individually directed, be integrated into health care settings or offered by community agencies.

⁴ <http://healthypeople.gov/2020/about/DisparitiesAbout.aspx>.

Prevention – In the pain context, *primary prevention* are efforts to reduce injuries or diseases that may result in pain. *Secondary prevention* are interventions designed to reduce the likelihood that acute pain transitions into chronic pain. *Tertiary prevention* interventions attempt to limit the development of disabilities and other complications of chronic pain after it has developed.

INTRODUCTION

The sensory and emotional experience of pain plays an important protective role in human health and well-being, by alerting a person to actual or potential physical injury. Often, painful symptoms can be self-managed while the underlying cause resolves or is treated and recovery occurs. Such instances generally require little or no professional intervention. By contrast, when acute pain does not resolve, it may be associated with a serious disease, condition, or injury that needs timely medical care. When it persists, even after any identifiable underlying cause is resolved, it may signal that pain-initiated changes in the central nervous system have occurred. If so, the chronic pain is no longer a symptom of another disorder and has become the disease itself. And, like any disease, it requires appropriate treatment.

Chronic pain is a complex biopsychosocial phenomenon that may interfere with many aspects of a person's life—ability to work, personal relationships, and both physical and mental health. Chronic pain also is linked to premature death. Unchecked, secondary psychosocial and physical problems can worsen pain reciprocally, posing escalating threats to health and well-being, and various studies indicate the suicide rate among those living with chronic pain is higher than that of the general population.

Many factors influence the way specific patients perceive pain and adapt to it, the likelihood they will seek—and get—care, and their responses to treatment. These factors include past experiences, familial and genetic factors (including race and gender), comorbidities, cultural background, psychology, economic, and environmental factors. Despite this complexity, pain education, research, and treatment historically have focused on the pathophysiological mechanisms involved in chronic pain. This approach inadvertently encourages a “magic bullet” approach to treatment, deemphasizing the many other factors that, if overlooked, may render treatment and rehabilitative efforts futile.

An estimated 100 million Americans have some level of chronic pain. Severe, disabling chronic pain—in this report termed “high-impact chronic pain” (see Box 1)—affects a smaller, but significant proportion of the population. Because people with chronic pain may not seek treatment, it is important to assess the prevalence and consequences of chronic pain among people in the general population as well as those who seek medical attention. More precise assessments of the incidence, prevalence, and significance of pain in the U.S. population are needed in order to establish a reliable basis for population-wide interventions and a baseline for assessing efforts to relieve the physical, psychological, social, and economic burdens of pain.

Certain pain conditions are known to affect population groups differentially, and some groups—whether defined by age, sex, gender, race/ethnicity, geographic isolation, socioeconomic status, or other characteristics—have less access to pain prevention, assessment, and treatment services and experience worse

outcomes. These barriers reflect systemic challenges, and many are driven by current reimbursement policies, provider attitudes and training, stereotyping, and biases. In addition, chronic pain is a costly problem. It engenders high direct medical care costs, as well as costs associated with disability programs, lost productivity, and family burden. According to the IOM report's estimates, this total is between \$560 billion and \$635 billion annually.⁵

Viewing chronic pain from a public health perspective allows patients, families, clinicians, and policymakers to benefit from available public health knowledge and disease models and adds precision to the concept of pain prevention. This melding of public health mindset and individualized treatment offers the best chance to improve all Americans' access to high-quality and more cost-effective pain care. Where gaps exist, this approach may point to areas where basic biomedical and translational research is needed.

People living with chronic pain who seek care face many hurdles. Wide variability exists in clinical practices related to prevention, assessment, and treatment. Acute pain not managed properly may develop into chronic pain, and, according to the IOM report, most Americans who live with chronic pain do not receive appropriate care. What care is provided is often fragmented, without a comprehensive assessment or treatment plan, and patients may encounter difficulty obtaining the full range of potential treatments. The widespread use of unnecessary diagnostic tests and procedures and relatively ineffective and potentially harmful treatments has been linked to high health care costs.

Public health concerns related to the misuse or diversion of prescription pain medications add another layer of complexity to the management of chronic pain. As part of a public health effort over the past few decades to improve pain management, a broader prescribing of opioids led to a significant rise in adverse health consequences, including addiction, abuse, and overdose. Prescriber practices drove a steady and significant increase in the number of opioid prescriptions dispensed, rising from 76 million in 1999 to 219 million in 2011⁶. The amount per prescription, the duration of the supply, and the cumulative dose prescribed also increased.⁷ These dramatic increases paralleled rises in opioid-related substance abuse treatment admissions⁸ and rates of opioid-involved overdose deaths, which reached over 16,000 in 2010.⁹ Studies have identified patient risk

⁵ These cost estimates were based on the U.S. adult non-institutionalized civilian population and, therefore, exclude children, prisoners, people in nursing homes or other institutional settings, and the military.

⁶ IMS Health, Vector One: National, Years 1991-1996, Data Extracted 201. IMS Health, National Prescription Audit, Years 1997-2013, Data Extracted 2014.

⁷ Kenan K. Mack K, Paulozzi L. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000-2010. *Open Med.* 2012;6(2):41-47. <http://www.drugabuse.gov/related-topics/trends-statistics/monitoring-future>

⁸ Substance Abuse and Mental Health Services Administration. Drug Abuse Warning Network, 2007: national estimates of drug-related emergency department visits.

⁹ Mack, K.A. Drug-induced deaths - United States, 1999-2010. *MMWR Surveill Summ.* 2013 Nov 22;62 Suppl 3:161-3. CDC

factors for overdose. Understanding these factors is important to enable the identification of populations at highest risk as well as for the development of interventions that target these high-risk groups.

The reluctance of many clinicians to prescribe these medications, and patients' concerns over stigmatization associated with opioids may jeopardize quality pain control in the population. Only a small percentage of practitioners and patients account for the majority of opioid-related risk through abuse of prescribing privileges and inappropriate management of prescriptions¹⁰.

Prescription opioids for management of moderate to severe pain are recommended in clinical practice guidelines for chronic pain management in selected patients. They are considered medically appropriate and safe for acute and for intractable pain that is not adequately managed with other methods, when used as prescribed. A recent conference¹¹ to assess the safety and efficacy of long-term opioid use for chronic pain concluded that there are insufficient data to guide appropriate patient assessment, opioid selection, dosing strategies, or risk mitigation and noted the need for further research on the effectiveness of long-term opioid use for chronic pain. The panel also concluded that opioids are an essential component of optimal treatment for some patients and noted the challenge of identifying those who will benefit and are at low risk for adverse effects. The conference highlighted the need for more research and development to ensure that pain management is team based, individualized, multidisciplinary, and patient centered. Access to safe and effective care for people suffering from pain remains a priority that needs to be balanced in parallel with efforts to minimize the harms from opioids.

Effective pain control strategies emphasize shared decision-making, informed and thorough pain assessment, and integrated, multimodal, and interdisciplinary treatment approaches that balance effectiveness with concerns for safety. Opportunities for improvements in care may arise with the increasing emphasis on team-based care and care coordination, facilitated by the adoption of electronic health records, along with continued health services delivery research and implementation of better models. More effective delivery of services, supported by appropriate system characteristics and reimbursement, are essential to the "cultural transformation" called for in the IOM report, though far from the norm today.

While the development of better treatments and care models for chronic pain conditions is a high priority, at the same time, no opportunity should be lost to *prevent* the conditions and events that lead to chronic

¹⁰ Blumenschein K, Fink JL, Freeman PR, et al. Independent evaluation of the impact and effectiveness of the Kentucky All Schedule Prescription Electronic Reporting Program (KASPER). Available at: <http://chfs.ky.gov/NR/rdonlyres/24493B2E-B1A1-4399-89AD-1625953BAD43/0/KASPEREvaluationFinalReport10152010.pdf> Accessed October 2012.

¹⁰⁹ Oregon Health Authority. Prescription drug dispensing in Oregon. October 2011-March 2012. Available at http://www.orpdmp.com/orpdmpfiles/PDF_Files/Reports/Statewide_10.01.11_to_03.31.12.pdf.

¹¹ Pathways to prevention https://prevention.nih.gov/docs/programs/p2p/ODPPainPanelStatementFinal_10-02-14.pdf

pain and to intervene early with evidence based care, before acute pain becomes chronic. Even though pain is a leading cause of primary care visits, clinicians are generally under-trained in ways to assess and manage pain effectively. Improvements in professional education about state-of-the-art care for pain, in all its dimensions—including better communication, empathy, and cultural sensitivity—will yield significant care improvements.

A robust public education effort may lend support to individuals with pain, as well as to the dedicated clinicians, researchers, and advocates working to prevent and reduce the impact of pain among Americans. This effort will improve understanding of chronic pain and its significance among individuals, families, and society and increase knowledge about the availability of more effective treatment approaches.

The U.S. health care system is evolving toward a model that is patient-centered, evidence- and outcomes-guided yet individualized, and provided through high-performance, interdisciplinary care teams. This evolution suggests that development of a National Pain Strategy is remarkably timely. However, to be successful, this model must more effectively address the common complaint of pain. Recognition of need for improvements in pain care, along with appreciation of pain’s enormous human and economic burden, led the IOM Committee to develop a set of underlying principles (Box 2) that likewise informed development of this National Pain Strategy.

Box 2

IOM Committee Underlying Principles*

- ***A moral imperative.*** Effective pain management is a moral imperative, a professional responsibility, and the duty of people in the healing professions.
- ***Chronic pain can be a disease in itself.*** Chronic pain has a distinct pathology, causing changes throughout the nervous system that often worsen over time. It has significant psychological and cognitive correlates and can constitute a serious, separate disease entity.
- ***Value of comprehensive treatment.*** Pain results from a combination of biological, psychological, and social factors and often requires comprehensive approaches to prevention and management.
- ***Need for interdisciplinary approaches.*** Given chronic pain’s diverse effects, interdisciplinary assessment and treatment may produce the best results for people with the most severe and persistent pain problems.
- ***Importance of prevention.*** Chronic pain has such severe impacts on all aspects of the lives of people who have it that every effort should be made to achieve both primary prevention (e.g., in surgery for broken hip) and secondary prevention (of the transition from the acute to the chronic state) through early intervention.
- ***Wider use of existing knowledge.*** While there is much more to be learned about pain and its treatment, even existing knowledge is not always used effectively, and thus substantial numbers of people suffer unnecessarily.
- ***The conundrum of opioids.*** The committee recognizes the serious problem of diversion and abuse of opioid drugs, as well as questions about their usefulness long-term, but believes that when opioids are used as prescribed and appropriately monitored, they can be safe and effective, especially for acute, post-operative, and procedural pain, as well as for patients near the end of life who desire more pain relief.

- ***Roles for patients and clinicians.*** The effectiveness of pain treatments depends greatly on the strength of the clinician-patient relationship; pain treatment is never about the clinician’s intervention alone, but about the clinician and patient (and family) working together.
- ***Value of a public health and community-based approach.*** Many features of the problem of pain lend themselves to public health approaches--a concern about the large number of people affected, disparities in occurrence and treatment, and the goal of prevention cited above. Public health education can help counter the myths, misunderstandings, stereotypes, and stigma that hinder better care.

*Institute of Medicine, 2011, *op. cit.*, p. 3.

Population Research

Publication of the 2011 report by the Institute of Medicine, *Relieving Pain in America*, has led to growing recognition of the impact of pain on the health, productivity, and well-being of the U.S. population. Efforts to lower the impact of chronic pain at the individual and population levels need to be guided by population-based data. At present, data are needed on the prevalence, onset, course, impact, and outcomes for most common chronic pain conditions. These data will help guide policies and initiatives of federal and state governments, and of health care organizations and insurers.

A core responsibility of public health agencies is assessing the significance of health problems in the population. These calculations typically reflect a problem’s incidence, prevalence, and severity (morbidity, associated mortality, and disability) in the population as a whole and in relevant groups, defined by demographic characteristics, geography, or other parameters of interest. For chronic pain, better data are needed to understand the scope of the problem and to guide action, including efforts to reduce the impact of chronic pain through primary, secondary, and tertiary prevention. Such estimates of impact are needed in order to define health care workforce and service delivery needs and priorities for insurance benefits, as well as for monitoring the quality, safety, effectiveness, and costs of relevant programs and policies. Population research is, therefore, an essential tool in the implementation of this National Pain Strategy.

The World Health Organization's International Classification of Functioning, Disability and Health (ICF) considers determinants of health and disability from the perspective of the biopsychosocial model.¹² The following ICF concepts are relevant to defining chronic pain:¹³

Impairments: Problems with body structure or function

Activities: The execution of a task or action by an individual

Activity limitations: Difficulties an individual may have in executing activities

Participation: Involvement in a life situation

Participation restrictions: Problems experienced in life situation or social role involvement

Three inter-related manifestations of chronic pain define its overall individual and societal impact: perception, activity limitations, and participation restrictions. Lower to intermediate levels of pain severity are less likely to significantly impact social, recreational and vocational functioning, while more severe levels are associated with activity limitations and participation restrictions. The IOM report emphasized that chronic pain is common, affecting over 30 percent of the adult population to some extent. It is therefore critically important to differentiate people with *high-impact chronic pain* from those who sustain normal activities although experiencing chronic pain. Accordingly, the pain assessment tools proposed for population research in chronic pain (Appendixes D-F) are designed to identify people in the general population who suffer from chronic pain at various levels of severity, including those who have *high-impact chronic pain* based on the degree to which pain limits their ability to participate in work, social, or self-care activities.

The pain assessment tools proposed for population research use the definitions of chronic pain and high-impact chronic pain, which are based in part on the widely used definition of chronic pain recommended by the International Association for the Study of Pain,¹⁴ modified to account for intermittent pain.

Chronic pain is pain on at least half the days for six months or more.

High-impact chronic pain is associated with substantial restriction of participation in work, social, and self-care activities for six months or more.

¹² World Health Organization. International Classification of Functioning, Disability and Health. World Health Organization, Geneva, 2001.

¹³ For example: Tucker CA, Cieza A, Riley AW, Stucki G, Lai JS, Ustun TB, Kostanjsek N, Riley W, Cella D. Concept analysis of the Patient Reported Outcomes Measurement Information system (PROMIS) and the International Classification of Functioning, Disability and Health (ICF). *Qual Life Res* 2014, Epub ahead of print; Stier-Jarmer M, Cieza A, Borchers M, Stucki G, World Health Organization. How to apply the ICF and ICF core sets for low back pain. *Clin J Pain* 2009; 25:29-38; Leonardi M, Steiner TJ, Scher AT, Lipton RB. The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). *J Headache Pain* 2005; 6:429-40; and Stucki G, Ewert T. How to assess the impact of arthritis on the individual patient; the WHO ICF. *Ann Rheum Dis* 2005; 64:664-8.

¹⁴ International Association for the Study of Pain. (1986). *Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Pain Suppl*, 3, S1-226.

The Problem: Improvements in data methods and measures are needed to:

(1) guide efforts to reduce the burden of chronic pain through more accurate estimates of the prevalence of chronic pain and high-impact chronic pain in the general population and within population groups defined by demographic factors (age, gender, race, ethnicity, education, and socioeconomic status) and geographic areas, including identification of risk factors that predispose towards the development of chronic pain;

(2) provide standard methods for the analysis of electronic health care data related to pain treatment, which can reveal patterns of health services utilization, including over- and under-treatment, costs, and, most important, quality of care;

(3) develop a system of metrics for tracking changes in pain prevalence, impact, treatment, and costs over time that will enable assessment of progress, evaluation of the effectiveness of interventions at the population health level—such as public education or changes in public policy, insurance benefits, treatments, and organization of care—and identification of emerging needs.

The intent of the population research component of the National Pain Strategy is to provide methods and measures to guide progress towards achieving improved prevention (primary, secondary, and tertiary) and management of pain in the United States.

Objective 1: Estimate the prevalence of chronic pain and high-impact chronic pain in the general population and in primary care settings, both overall and for anatomically defined pain conditions and for various population groups.¹⁵

Short-term strategies and deliverables:

- Test a set of proposed pain screener questions (Appendix D) and brief self-assessment questions about high-impact chronic pain (Appendix E) in a representative population sample and among those whose pain treatment pattern suggests high-impact chronic pain is likely.
- Convene key stakeholders to review questions related to pain in current national population surveys¹⁶ and make recommendations regarding the appropriateness of standardizing, adding, or

¹⁵ Stratified by age, gender, race and ethnicity, education, socioeconomic status, health status, and indicators of biopsychosocial resiliencies and vulnerabilities.

¹⁶ Including the National Health Interview Survey (NHIS) and the National Health and Nutrition Examination Survey (NHANES), as well as Behavioral Risk Factor Surveillance System surveys, the Health and Retirement Survey, the Medicare Current Beneficiary Survey, and other regular and special supplemental population-based pain research appropriate for this purpose.

revising questions to bring these surveys in line with the NPS-proposed self-assessment questions in Appendixes D and E.

- Conduct additional evaluative studies of the NPS-proposed self-assessment questions and any alternative questions including cognitive testing and translation into other languages.
- Prepare a manuscript for submission to a peer-reviewed journal reporting the results of the test of the proposed brief pain self-assessment questionnaire.

Medium-term strategies and deliverables:

- Convene key stakeholders to refine self-assessment questions and measurement strategies and to build support for and facilitate implementation of the proposed population-based measurement and evaluation components of the National Pain Strategy.
- Incorporate a brief pain self-assessment questionnaire resulting from this process into at least one national morbidity survey and schedule initial implementation of data collection using these items.

Longer-term strategies and deliverables:

- Use the increasingly refined measures developed to evaluate longitudinal pain outcomes among Medicare, Medicaid, and other beneficiaries, including in post-acute care evaluations, the Minimum Data Set, and other comparable population-based tools.

Stakeholders and collaborators: Agency for Healthcare Research Quality (AHRQ), Centers for Disease Control and Prevention (CDC), Department of Defense (DoD), NIH, Veterans Health Administration (VHA), and other entities involved in population-based research for finalizing pain assessment questions); Centers for Medicare and Medicaid Services (CMS) and other entities concerned with the impact of pain, such as public and private health insurers, employers, and researchers; health care provider and professional organizations; patient advocacy organizations and people with pain.

Metrics: Agreement reached on a brief set of validated pain-related questions and their incorporation into population research going forward.

Objective 2: Refine and employ standardized electronic health care data methods to determine the extent to which people with common pain conditions, including those from vulnerable groups, receive various treatments and services, the costs of these services, and the extent of use of treatments that best evidence

suggests are underused, overused, effective, and ineffective.

Short-term strategies and deliverables:

- Carry out proof-of-concept analyses with large health care databases to identify patterns of pain treatment among people in specified diagnostic clusters¹⁷ (Appendix F) and their associated costs. This activity would provide insights regarding disparities in pain care, as well as how different reimbursement models affect both patterns of treatment and costs.
- Prepare a manuscript for submission to a peer-reviewed journal reporting the results of the proof-of-concept analyses of health care data on diagnostic clusters and pain treatment indicators and related recommendations.
- Encourage the Centers for Medicare and Medicaid Services to make adequate pain measures a component of its incentive programs for establishing “meaningful use” of electronic health records, an action deemed especially helpful in monitoring care for vulnerable populations.

Medium- to longer-term strategies and deliverables:

- Refine the initially proposed diagnostic clusters and treatment indicators, including adaptation of the diagnostic clusters to ICD-10 nomenclature.
- Convene key stakeholders to consider standardization and widespread use of the resulting diagnostic clusters and treatment indicators in population research using electronic health care data. Ideally, the resulting analyses would be accompanied by evidence-based characterization of treatment indicators (Appendix G), including the relative value of specific pain treatments, as emphasized in the Service Delivery and Reimbursement section
- Establish a pain research network to study risk factors for the initiation and maintenance of chronic pain and high-impact chronic pain and patterns of pain treatment using the diagnostic clusters and pain treatment indicators.¹⁸ Use the network to develop data on trends in pain treatment in different population groups, including evidence of under-treatment, and costs of specific pain treatment services and to identify opportunities and priorities for primary prevention.

¹⁷ Diagnostic clusters refer to clinical groups of painful conditions, grouped on the basis of anatomical location of the pain rather than diagnostic specificity. They allow analysis of electronic data on use of health services for common pain conditions in clinically meaningful groups (e.g., back pain, headache).

¹⁸ Recognizing that these categories are subject to continued refinement based on experience, new research findings, and external factors, such as the implementation of ICD-10.

Stakeholders and collaborators: For the proof-of-concept analyses and the pain research network: AHRQ, Office of the National Coordinator for Health Information Technology (ONC), NIH, and other relevant entities; evidence-based practice centers in universities; relevant primary care and specialty professional societies; CMS, DoD, VHA and other public and private sector health care financing and delivery systems that have large patient and health maintenance organizations; health insurers; patient advocacy organizations; and people with pain.

Metrics: quantity, quality, and usefulness of publications arising from the research network; adoption of diagnostic cluster and pain treatment indicator methodology within and outside government-funded programs.

Objective 3: Develop a system of metrics for tracking changes in pain prevalence, impact, treatment, and costs over time that will enable assessment of progress, evaluation of the effectiveness of interventions at the population health level—such as public education or changes in public policy, payment, and care—and identification of emerging needs. Apply these metrics to evaluate the effectiveness of primary, secondary and tertiary prevention interventions. These initiatives may include public policy initiatives, demonstration projects in the organization or reimbursement of care, or public education efforts.

Short -term strategies and deliverables:

- Set measurable goals for reducing the prevalence of high-impact chronic pain and for increasing the value of health care and preventive services for chronic pain to be incorporated into Healthy People 2020.
- Coordinate across the federal agencies that gather data related to primary prevention strategies (primarily injury prevention and improved management of certain chronic conditions).

Medium-term strategies and deliverables

- Develop approaches to assessing pain's impact in longitudinal studies that consider pain perceptions, activity limitations, and participation restrictions in work, social and self-care roles, work productivity, utilization of disability benefits and other services, family effects, and utilization and costs of health care services.
- Evaluate outcomes of Healthy People 2020 chronic pain to inform and guide appropriate objectives/questions for a dedicated chronic pain objective to be included in HP 2030.

Longer-term strategies and deliverables:

- Encourage health care providers and insurers to use data developed under these initiatives and the collaborative relationships established to:
 - guide enhancements to health care and preventive services and
 - evaluate the effectiveness of interventions at the population health level, such as public policy initiatives, demonstration projects in the organization or reimbursement of care, or public education efforts.¹⁹

Stakeholders and collaborators: CDC, DoD, NIH, VHA, and other relevant public and private entities that collect data on pain and its treatment, disability program utilization, and other public benefits; employer and employee organizations; AHRQ, CMS, DoD, VHA, and other relevant public and private entities involved in health services research, care delivery, financing, and program evaluation; and patient advocacy organizations and people with pain.

Metrics: extent of adoption of the pain assessment and treatment metrics and their use in assessing programmatic interventions; adoption of the proposed measures in the Healthy People data tools and reporting system; extent of use in program planning, implementation, and evaluation at the community, state, and federal levels.

Prevention and Care

Preventable causes of acute and chronic pain should be identified and addressed throughout the health care delivery system. When acute pain from injury or disease is present, or when a persistent pain state has developed, clinicians should assess and comprehensively manage it using practice guidelines based upon best available evidence of effectiveness. Current opportunities to manage the continuity of care during transitions across health care settings and to expand real-time access to a carefully selected and synthesized body of relevant evidence should be enhanced in order to improve coordination of care and optimal use of resources.

¹⁹ Washington State's Bree Collaborative (see <http://www.breecollaborative.org/about>) provides a model for such collaboration. For example, the Bree Collaborative recently developed strategies to enhance the value of health care for low back pain (see <http://www.breecollaborative.org/topic-areas/spine>).

To date, the quality and quantity of evidence guiding clinical approaches to the prevention, assessment, and treatment of pain have lagged behind that for treatment of other major disease and public health burdens, such as cancer, infectious diseases, and cardiovascular disease. Given that acute pain can progress to chronic pain which is a disease in itself, certain principles, are clear:

- evidence-based care approaches should follow the public health prevention model and address primary, secondary, and tertiary prevention
- evidence-based pain care should involve an interdisciplinary team approach and cover the different levels of pain care—from prevention to self-care to acute to chronic pain management—as needed, and
- high-quality pain care should be available in all settings and at all levels of care, from primary care to interdisciplinary pain care centers, as the intensity of pain management efforts increases.

The Problem: Chronic pain may begin with an injury, or procedure that evolves into a persistent painful condition. Often, however, the cause of its onset is uncertain, and the mechanisms by which it persists are complex. There is a great need to better understand the factors that cause pain to become persistent and to develop and apply measures to prevent acute pain from transitioning to a chronic state. Opportunities to prevent acute to chronic pain progression depend not only on the nature of the initial insult and treatment, but also upon various patient-related risk factors. While there is much more to be learned about chronic pain prevention and treatment, existing knowledge could be used more effectively to reduce substantially the numbers of people who suffer unnecessarily. Most people who have pain do not receive appropriate assessments or evidence-based care that is coordinated across providers and individualized for specific higher-risk situations. A robust basic, translational, and health services research effort is needed to validate the effectiveness of pain prevention and management strategies already in use, and to develop new ones.

The intent of the Prevention and Care component of the National Pain Strategy is to advance evidence-based, culturally sensitive and individualized prevention and care of pain, using the biopsychosocial model and providing value determined by accepted, validated, and systematically collected outcomes.

Objective 1: Characterize the benefits and costs of current prevention and treatment approaches. A thorough benefit-to-cost analysis of current prevention and treatment approaches, including self-management methods and programs, should be performed to identify and create incentives for use of interventions having high benefit-to-cost ratios. Conversely, treatments with little absolute benefit or a low benefit-to-risk ratio should be identified through clinical studies and efforts made to dis-incentivize their use. In judging the benefit of many treatments, clinicians and payers should bear in mind that an individual may belong to a specific population group in which the treatment may be either more beneficial (or more risky) than in the population at large.

Short-term strategies and deliverables:

- Perform a benefit-to-cost analysis of methods to prevent and treat pain for which the best available evidence suggests benefit. Such an analysis may help guide the choice between therapies that are equally efficacious but whose cost differs.
- Prepare a manuscript for submission to a peer-reviewed journal reporting the results of the benefit-to-cost analyses of current prevention and treatment approaches and related recommendations.
- Develop a best-estimate synthesis of causes of preventable injuries nationwide, including both workplace and non-workplace related accidents and physical trauma by:
 - Identifying areas where more evidence is needed (for example, occupational injuries may be substantially underreported²⁰)
 - Reviewing existing programs for primary prevention and the evidence for their effectiveness, and
 - Estimating the number of people with chronic pain whose condition is preventable as a first step in developing more robust preventive efforts.
- Begin research efforts geared toward development of new prevention and treatment methods likely to have high benefit-to-cost ratios.

Medium-to-longer term strategies and deliverables:

- Incorporate the most effective and cost-efficient treatments into practice guidelines and other best practices efforts (for example, the Physician Quality Reporting System), with inclusion of standards-based clinical decision support to enable providers and patients to make decisions in line with best practice guidelines. followed by:
 - Assessment of insurer practices that either deny payment for effective and cost-efficient treatments for patients who could benefit from them or continue to reimburse less effective ones.
- Development of a framework for measuring treatment outcomes on pain, level of disability, and the full range of psychosocial impacts.

Stakeholders and collaborators: AHRQ, ONC, the National Institute for Occupational Safety and Health, the Occupational Safety and Health Administration, the VHA, and other relevant federal and private entities; public, including CMS, and private insurers; patient advocacy organizations and people with pain.

²⁰ U.S. Government Accountability Office. 2009. Enhancing OSHA's records audit process could improve the accuracy of worker injury and illness data. GAO-10-10, p. 19. See also Figures 12 and 13. Accessed June 27, 2014, from <http://www.gao.gov/assets/300/298510.pdf>.

Metrics: the level of integration of effective, cost-efficient pain treatments into the health care system and the impact on outcomes for people with pain; extent of dissemination of these results to health care providers, payers, and policymakers.

Objective 2: Develop nation-wide pain self-management programs.²¹ Despite evidence to support team-based, pain self-management programs for pain, their implementation has lagged, which represents an unmet opportunity to provide people with pain the appropriate skills, education, and resources to play an active role in managing their pain, which includes understanding when clinical consultation is needed. These programs should be integrated into the health care system to bolster their use and prevalence and to guide patients through the several levels of pain care. Goal setting (action planning), problem solving, decision making and psychosocial aspects of care should be included in the programs.

Short-term strategies and deliverables:

- Perform an environmental scan of pain self-management programs that²²
 - cover the continuum of prevention and pain; foster skills to prevent, cope with, and reduce pain; and provide people having pain with the practice and confidence to utilize the core self-management skills of goal setting (action planning), problem solving, and decision making
 - are offered in differing health care settings, by community agencies, patient advocacy organizations, or that stand alone, and
 - are culturally neutral, allowing each group or individual to self-tailor the intervention, and are available in multiple languages, as well as in audio versions for those with low literacy.

Medium-term strategies and deliverables:

- Evaluate the efficacy of existing pain self-management programs and support research and development of new programs and models, as necessary, to address the continuum of pain.
- Leverage existing programs, such as the extensive self-management tools for patients with chronic disease.²³

²¹ See definitions, Box 1. In addition, to meet people's various circumstances and learning preferences, self-management programs must be offered in multiple models (in groups of varying sizes, electronically via smartphone or computer, by mail, or by telephone).

²² Specific programs that warrant an evaluation include the American Chronic Pain Association's program, Stanford Patient Education Research Center Programs, CDC's osteoarthritis program, and model falls prevention programs.

²³ Examples of program models include: Stanford's Patient Education Research Center; CDC's Arthritis Self-Management Program; the University of New Mexico's telehealth program, ECHO; the A Matter of Balance program developed by Boston University; or the National Institute of Neurological Disorders and Stroke's program for pediatric migraine, under development.

- Develop new types of patient tools for pain management and provider feedback using, for example, mobile applications, that also integrate with electronic health records (EHRs), personal health records (PHRs)/patient portals, wearable devices, and other technologies.

Longer-term strategies and deliverables:

- Implement, evaluate, and disseminate nationally evidence-based pain self-management programs that are effective, as documented by high-quality research methods, and that have developed materials and a structure enabling them to be transferred to one or more additional sites.
- Encourage the inclusion of evidence-based programs as covered benefits under public and private integrated health systems, including the VHA, especially for people with indicators or risk factors for transitioning to chronic pain.
 - Include information on effective pain self-management programs in various health information directories, such as <http://www.health.gov/> and non-governmental resources for patients.
 - Through various means, direct those with the indicators or risk factors for transitioning to chronic pain to effective self-management programs.

Stakeholders and collaborators: AHRQ, DoD, and VHA in collaboration with HRSA (as appropriate to their statutory priorities and within their authority), and other relevant federal agencies, the Patient-Centered Outcomes Research Institute (PCORI) and private entities that support health care assessments and outcomes monitoring; professional organizations; public and private payers, health care provider organizations, and other potential funders (to ensure a vigorous and widely supported effort); patient advocacy organizations; and people with pain.

Metrics: outcomes data obtained by leveraging established tools, such as the NIH and Department of Defense’s collaborative PASTOR/PROMIS system, the NIH Pain Consortium, Stanford University’s Collaborative Health Outcomes Information Registry (CHOIR), and those developed by the Joint Commission; and by innovative use of data from electronic health records

Objective 3: Develop standardized, consistent, and comprehensive pain assessments and outcome measures across the continuum of pain. Pain assessment should be multifaceted and include self-report, as

well as clinician examination. Assessment and outcomes measures should include relevant pain, physical, psychological, and social domains of functioning that conform to the biopsychosocial model of pain, as well as patient-reported outcomes and patient-defined goals. Assessments and outcomes should be used for point of care decision-making by clinicians, longitudinal outcomes monitoring, estimations of value of alternative treatment approaches, and practice-based effectiveness studies.

Short-term strategies and deliverables

- Develop comprehensive quality assessments and outcome measures for the continuum of pain.
 - Establish expert working groups to survey and identify gaps in available assessment and outcomes tools for the continuum of pain, including both general assessments and condition-specific modules, especially taking into consideration their usefulness for primary care providers and for population research.²⁴
 - Conduct research and developmental studies to create new assessment tool models identified as needed.
 - Integrate appropriate pain self-assessment tools into EHR patient portals to aid providers and patients in clinical decision making.
 - Recommend ways to integrate outcomes measures into existing assessment systems, as necessary.

Medium-term strategies and deliverables

- Disseminate existing assessment tools and outcome measurement systems that prove most effective and are easily managed, and create incentives for using them.
- Conduct pilot studies of new models that emerge from research.

Longer-term strategies and deliverables

- Evaluate the benefits and costs of improved, standardized assessment tools and outcome measures.

Stakeholders and collaborators: AHRQ, CDC, CMS, NIH, and other relevant federal and private entities including PCORI; public and private insurers; professional organizations (especially primary care); pain advocacy organizations; and people with pain.

Metrics: the extent of adoption of improved assessment tools and outcome measurement systems.

²⁴ The NIH Task Force on Research Standards for Chronic Low Back Pain is an example of such a task force.

Disparities

The IOM report, a large body of research, patient reports and other sources indicate that substantial disparities in pain occurrence, assessment, treatment, and outcomes are common; U.S. data indicate a greater prevalence of pain conditions among specific population groups typically of interest to public health programs. The Healthy People definition of disparities, included in the Background section of the strategy, describes these groups. When this section of the National Pain Strategy discusses bias, stigma, and discrimination, it is referring to all higher-risk groups that comprise vulnerable populations.

While many factors affect an individual's experience of pain and willingness to seek or adhere to treatment, and while more comprehensive efforts are needed to prevent pain in higher risk groups, this section of the National Pain Strategy focuses on improving the quality of pain care for vulnerable populations, especially as it may be affected adversely by provider attitudes and behavior that result in discrimination, bias, or stigma, which themselves can lead to or exacerbate pain. Examples of patient groups and conditions for which bias has been reported are diverse and widespread and include: women exhibiting pain from chronic fatigue syndrome, fibromyalgia, and other conditions; elderly patients in nursing home settings; minority patients with sickle cell disease or pain associated with human immunodeficiency virus (HIV) infection

Pain care disparities are complex, due to myriad contributing factors within and outside the health care sector. Eliminating disparities and promoting equity in pain care cannot be achieved without increased access to high-quality pain treatment, developing strategies and expectations for equitable assessment and treatment of pain, and appropriate supporting programs and services (such as disability programs) for people with pain. Also needed is improved communication between service providers and people with pain and their families.

The Problem: A significant problem facing vulnerable populations arises from conscious and unconscious biases and negative attitudes, beliefs, perceptions, and misconceptions about higher-risk population groups (e.g. gender or racial bias) or about pain itself. If held by clinicians, social service program administrators, or other decision-makers, these attitudes can negatively affect the care and services they provide. For example, inappropriate or inadequate treatment may result if clinicians fail to understand or to accept that individuals differ in pain sensitivity and treatment response due to a wide range of factors. People with pain who encounter these biases can feel stigmatized, which may decrease their willingness to report pain in a timely way, participate in decisions about their care, adhere to a recommended treatment plan, or follow a self-care protocol. This perception also may negatively affect their psychological state.

An additional barrier to eliminating pain disparities is the lack of sufficient knowledge of behavioral and biological issues (e.g., genomic variability, pharmacokinetic and pharmacodynamic differences) that affect pain onset and management and data to understand patterns of pain and its treatment in higher risk and vulnerable populations.

The intent of the disparities component of the National Pain Strategy is to improve the quality of pain care and reduce barriers for all minority, vulnerable, stigmatized, and underserved populations at risk of pain and pain care disparities.

Objective 1: Reduce bias (implicit, conscious, and unconscious) and its impact on pain treatment by improving understanding of its effects and supporting strategies to overcome it.

Short-term strategies and deliverables:

- Document and expand the evidence base of adverse effects of clinician bias on the pain experience for use in developing, validating and implementing, clinician and public education, policy recommendations, and health system reforms:
 - Conduct a baseline survey of health care providers to assess their biases, attitudes, beliefs, knowledge, and behavior regarding pain among people from vulnerable populations.
 - Convene an expert group to review evidence on the impact of health care provider bias in decision-making on the pain experience (including effects on patients and treatment effectiveness) and the strategies to overcome bias (at the patient, clinician, institutional, and health system levels) and to identify gaps in knowledge. The gaps should serve as a starting point to formulate a research strategy to improve clinician education, pain care and management, and direct pain policy.

Medium-term strategies and deliverables:

- Convene an expert group to assess the role of health care provider bias in decision-making regarding integrated, multimodal, and interdisciplinary pain care, including analgesic and psychological treatment.
- Convene an expert group to assess the state of the science and promote a better understanding of biological variability, including genetic and other influences, affecting pain sensitivity and treatment response across diverse populations.
- Disseminate the proceedings of the groups to clinicians who treat pain through a manuscript in a relevant journal and other appropriate means.
- Based on the workshop recommendations and identification of evidence gaps, federal agencies should develop and support pilot projects in bias reduction.

Longer-term strategies and deliverables:

- Conduct demonstration projects based on the results of the pilot projects, to further test bias reduction strategies. These studies should be carried out in health care systems or other large population-based service delivery systems.
- Develop, implement, and evaluate policy recommendations and guidelines on bias reduction for clinicians, based on the recommendations of the work groups and the outcomes of the demonstration projects.

Stakeholders and collaborators: AHRQ, Office of Minority Health, NIH, and other relevant public and private entities; professional organizations, health care providers; and other policymakers; community representatives and patient advocacy organizations; and people with pain.

Metrics: extent of implementation of policy recommendations and guideline adoption; eventually, a repeat survey could assess any changes in health care provider practices and patient outcomes.

Objective 2: Improve access to high-quality pain services for vulnerable population groups.

Short-term strategies and deliverables:

- Promote awareness of current patient and provider resources that link people with chronic pain to care (e.g., programs and health centers, behavioral health providers, nursing homes, hospices, and clinician specialists).
- Develop demonstration projects of ways to improve access to current resources, including projects to determine the potential of patient-centered medical homes to serve people living with chronic pain who are at risk for disparities in care.

Medium-term strategies and deliverables:

- Develop an interactive web-based gateway to information and resources for patients and families, which could include a pain specialist locator, a link to <http://healthfinder.gov/>, and self-care tools.
- Develop demonstration projects to assess the usefulness of the information gateway in improving access to high-quality pain care among vulnerable populations.
- Promote and disseminate use of high-quality telemedicine consultations and training programs for hard-to-reach populations and for clinicians who do not practice where multidisciplinary colleagues are available.²⁵

Longer-term strategies and deliverables:

- Promote and disseminate effective models from the demonstration projects (new access models, web-based tools) through various means, and provide financial incentives to adopt them.

Stakeholders and collaborators: CMS, OMH, Indian Health Service (IHS) and other relevant public and private entities (for promoting awareness within existing programs, developing demonstration projects, and evaluating existing tools); other public and private health care provider organizations (especially public-funded centers and clinics, patient-centered medical homes, and accountable care organizations); professional organizations; community representatives, patient advocacy organizations, and people with pain (to aid in assessing the information gateway, individual tools, and other web-based information products).

²⁵ Examples are the University of New Mexico's Project ECHO and the University of Washington's telemedicine program.

Metrics: changes in prevalence of untreated or inadequately treated pain among vulnerable groups in demonstration project models; number of users of the information gateway and telemedicine consultation service and their feedback.

Objective 3: Facilitate communication among patients and health professionals.

Short-term strategies and deliverables:

- Create an expert group to review and make recommendations on effects of disparities in pain care, in order to heighten national awareness, reduce the stigma of pain and support a national research agenda. Disseminate findings to the general public, researchers, health care providers, and professional organizations.

Medium- and longer-term strategies and deliverables:

- Improve the quality and certification standards of translation services for patients with low English proficiency or who have low literacy, health literacy, or communications disabilities, consistent with culturally and linguistically appropriate services (CLAS) standards.
- Develop guidelines specific to pain care, consistent with CLAS standards.

Stakeholders and collaborators: AHRQ, OMH and other relevant federal agencies; health care credentialing agencies (certification standards and guidelines); health professional training programs and licensing bodies (promoting cultural competency).

Metrics: increased number of staff and quality translation services in pain care settings; establishment of reimbursement models for payment of direct translation and interpreters; increased dissemination of high-quality educational materials about pain in multiple languages and at various literacy levels.

Objective 4: Improve the quality and quantity of data available to assess the impact of pain on higher-risk population groups, including data on group members' access to high-quality pain care and the costs of disparities in pain care.

Short-term strategies and deliverables:

- Develop data standards and definitions that enable tracking of pain prevalence and treatment in the full range of vulnerable populations. These standards and definitions could be applied to electronic health records, population-level surveys, and relevant clinical research.
- Create an expert group to assess the current costs of pain care disparities, including costs that result from health care utilization, lost work or educational opportunities, and use of disability and other benefits.

Medium- and longer-term strategies and deliverables:

- Develop additional data standards for national surveys and electronic health records needed to include disability and functional status relevant to pain.
- Use current and new data standards as developed above to enable national studies of pain under-treatment among vulnerable populations and to assess progress toward eliminating it.

Stakeholders and collaborators: AHRQ, CDC, ONC, NIH, and other relevant public and private entities (for research using new or existing data sets and data collection standards); the pain research community, patient advocacy organizations, and people with pain (for input on data needs, adequacy, and usability).

Metrics: increase in the number of studies conducted and published using improved data and information on the impact of pain in vulnerable populations.

Service Delivery and Reimbursement

A primary objective in enhancing the delivery of quality pain care is to make optimal pain management tailored to the individual available to all. Wide variation in clinical practice and in patients' responses to therapies, along with repeated use of relatively ineffective and potentially risky treatments, has been linked to poor quality and high costs of pain care. Because commonly used single-modality treatments often fail as first-line therapies for chronic pain, attention among leaders in the field has shifted to improving pain assessment and delivery of integrated, multimodal, interdisciplinary care that is effective and safe. The IOM report reflected this shift by advocating consistent and complete pain assessments, reimbursement reform to foster coordinated interdisciplinary care, and greater support for primary care clinicians to deliver the most effective, safe, and timely care, including more opportunities for consultations with pain specialists. The recommendations of this workgroup support a framework for which the advances in prevention and care outlined in that section of the report can be provided to all individuals with pain.

The National Pain Strategy likewise endorses a population-based, disease management²⁶ approach to pain care that is delivered by integrated, interdisciplinary, patient-centered teams and is consistent with real-world experience. To succeed, the care model must shift from the current fragmented fee-for-service approach

²⁶ *Disease management* refers to a system of integrated, multidisciplinary interventions and communications for populations with chronic disorders in which self-care efforts are significant. (Disease Management Association of America. Disease State Management Definition. Accessed at www.dmaa.org/dm_definition.asp, March 30, 2006.)

to one based on better incentives for prevention (primary, secondary, and tertiary) and for collaborative care along the continuum of the pain experience—from acute to chronic pain across the lifespan, including at the end of life—at all levels of care and in all settings.

The Problem. Access to high-quality integrated care based on clinical evidence is hindered by many challenges, including a payment system that does not support optimal care. Pain management often is limited to pharmacological treatment offered by a single primary care practitioner or to procedure-oriented and incentivized specialty care that is not coordinated and not aligned with the best available evidence or expected outcomes. This situation is especially relevant for people with high-impact chronic pain, where integrated care is likely to be most effective. Even when interdisciplinary care is provided, creating and executing a care plan is often fragmented, with poor communication among clinicians and without consideration of patient preferences. The clinician or team’s choice of therapy may be based on practice experience or on insurance coverage, rather than one informed by a comprehensive pain assessment, clinical evidence or best practices.

More quality research is needed on the effectiveness of pain interventions, integrated care, models of care delivery, and reimbursement innovations. Also needed are more effective methods to disseminate research findings and incentives to incorporate them into clinical practice. The number of level-I studies (e.g. high-quality randomized controlled trials or prospective studies) in pain is low. Patient-reported outcomes are rarely collected outside of clinical trials. Observational data and registry studies sometimes lack detail and relevant outcomes. There is a need to increase the rate of drug discovery and to raise the level of evidence for treatments in the management of pain and improve the adoption of evidence-based pain management in clinical practice.

The incongruity between high-quality care recommendations and real-world clinical practice is only partly the result of limited evidence to support existing clinical guidelines, however. Current reimbursement practices complicate development of a population-based approach that would use integrated, interdisciplinary, patient-centered teams. Payers tend to provide incentives for mono-therapy and interventional procedures instead of services that conform to the biopsychosocial model of care and incorporate pain self-management programs,²⁷ patient and family education, patient decision making, coordinated team-based medication management, counseling, cognitive-behavioral therapy, physical medicine and rehabilitation, and complementary health approaches. Current reimbursement mechanisms (see Appendix H) tied to the fee-for-

²⁷ *Self-management* includes nutrition and weight control, exercise and conditioning, sufficient sleep, mindfulness meditation and relaxation, engagement in meaningful activities, family and social support, and assuring a safe environment

service payment system also generally fail to support more value-driven approaches (for example, the stepped model of pain care²⁸ and other emerging models of coordinated care).

Further hurdles to quality pain care delivery are lack of access to and reimbursement for medications, managed primarily by retail pharmacies and third-party payers. Although analgesics should not be the sole intervention for most pain conditions, medications, including opioids, may be essential for improved quality of life. Rationing, medication shortages, and inadequate reimbursement for medication management and monitoring decrease patients' access to medications, causing considerable hardship, especially for vulnerable populations.

The overall, long-term intent of this component of the National Pain Strategy is to promote coordinated care across the continuum of pain in order to conform to the biopsychosocial model and provide value, as defined by outcomes of care.

Objective 1: Define and evaluate integrated, multimodal, and interdisciplinary care for people with acute and chronic pain, and end of life pain, which begins with a comprehensive assessment, creates an integrated, coordinated, evidence-based care plan in accord with individual needs and preferences and patient-centered outcomes, and is supported by appropriate reimbursement incentives.

Short-term strategies and deliverables:

- Convene expert stakeholders to promote interest in and greater understanding of the shortcomings in quality of care and the high costs of current pain treatment approaches, the existence of more effective models, and the steps that can be taken toward achieving high quality care and outcomes.

Medium-term strategies and deliverables:

- Solicit proposals through the Center for Medicare and Medicaid Innovation for pilot projects that evaluate emerging and innovative models of integrated care for chronic pain conditions.
- Engage stakeholders and potential collaborators to conduct rigorous evaluations of pilot projects in pain care, especially approaches using the stepped model of pain care, the biopsychosocial model,

²⁸ The *stepped model of pain care* (Appendix I) is a progression from self-management to primary care to specialty care to interdisciplinary pain care. The model is geared to outcomes and value, because, when treatment on one level of care produces satisfactory results for the patient, there is no need to progress to the next, more costly and intensive level. High-impact chronic pain, which suppresses a person's overall quality of life and ability to function, optimally is treated at the higher levels.

team-based care, pain self-management approaches, and care planning based on comprehensive pain assessments.

Longer-term strategies and deliverables:

- Monitor and evaluate outcomes of the pilot projects.
- Implement and evaluate optimal models in federal, state, and private provider contexts.

Stakeholders and collaborators: CMS, DoD, IHS, VHA, and other public and private entities that provide health care benefits (including PCORI; primary and specialty care clinicians; professional accreditation entities; integrated health care systems; large private third-party payers; pain advocacy organizations; and people with pain.

Metrics: Positive outcomes from pilot projects on measures of physical, psychological, and functional improvement for patients, as well as cost savings relative to conventional care; incorporation of validated, successful models into health care systems and clinical practice.

Objective 2: Enhance the evidence base for pain care and integrate it into clinical practice through defined incentives and reimbursement strategies, to ensure that the delivery of treatments is based on the highest level of evidence, is population-based, and represents real-world experience.

Short-term strategies and deliverables

- Develop and implement population-based studies designed to be cost-effective, represent real-world settings, including primary care practices and pain self-management programs, and include representative samples of patients that will provide practical approaches for assessing therapeutic effects. Evidence-based outcomes from these studies can be analyzed through available pain data registries, electronic health records, population surveys, and other appropriate data sources, including the tools recommended in the Population Research section.
- Leverage existing pain registries or initiate development of suitable new pain registries to track outcomes, including patient-reported outcomes, of the pilot projects in Objective 1, and develop, standardize and integrate process and outcomes measures into electronic health records, which may then be compiled across networks.

Medium-term strategies and deliverables:

- Compile results of the pilot projects in Objective 1, the population-based studies mentioned above, and those from the large national databases recommended in the Population Research section that are relevant to treatment choices.
- Disseminate these results to clinical audiences, quality improvement initiatives, public-private partnerships, patient and advocacy organizations, and others, in order to encourage implementation of more appropriate, evidence-based care.
- Inform the design of these research projects and integrate their findings with data obtained in the national survey activities described in the population research section of the National Pain Strategy.

Longer-term strategies and deliverables

- Expand the pilot pain registries to incorporate over time, findings from other studies, including randomized controlled trials, pragmatic trials, and other high-quality research methods.
- Convene expert stakeholders from appropriate disciplines to consider the outcomes of the pilot studies on emerging models of service delivery and reimbursement and to discuss adoption of consistent clinical guidelines on pain care across clinical specialties.
- Use population-based data to inform national policy for opioid use and monitoring, including comparative effectiveness of opioids versus other forms of treatment, effectiveness of state prescription drug monitoring and point-of-care interventions to prevent abuse and misuse, and the effects of regulatory and enforcement policies (Food and Drug Administration and Drug Enforcement Agency), on abuse, misuse, and access to opioid medications.

Stakeholders and collaborators: AHRQ, CDC, DoD, NIH, VHA, and other relevant public and private entities that support population-level research: PCORI; private payers, private agencies and software experts developing electronic medical records and other relevant programs, integrated health systems, and; health professions organizations, including credentialing bodies; primary care and specialty clinicians; pain advocacy organizations; and people with pain.

Metrics: incorporation of validated, successful models and practices from the pilot projects into provider practices and health care systems; outcomes of evaluated interventions and care, including patient and family assessments and costs, as compared to usual treatment; adoption of evidence-based practice guidelines for multiple disciplines.

Objective 3: Tailor reimbursement to promote and incentivize high-quality, coordinated pain care through an integrated biopsychosocial approach that is cost-effective, comprehensive, and improves outcomes for people with pain.

Short-term strategies and deliverables:

- Identify and invest in the development of models of care that deliver high-value pain care that simultaneously maximizes patient benefit and minimizes risk and costs.
- Identify, measure, and control variations in pain care that lead to low-quality or high-cost care.

- Develop new tools to facilitate payment for higher quality pain care.²⁹
- Define, identify, and engage eligible pain care clinicians willing to participate in quality and utilization reporting, including those participating in existing programs, such as the Medicare Physician Quality Reporting System.

Medium-term strategies and deliverables:

- Develop and test methodologies for defining episodes of care related to pain conditions to inform payment models and identify where pain should be included as a critical outcome of existing episode-based payment models.

Longer-term strategies and deliverables:

- Develop and support pilot projects to test and rigorously evaluate the impact of reimbursement innovations on pain care quality measures and cost savings.
- Disseminate results of the pilot projects to public and private payers for consideration in updating their reimbursement policies and practices.
- Develop clinical quality measures and clinical decision support for pain care.
- Make clinical quality measures for pain and associated decision support part of incentive programs.

Stakeholders and collaborators: relevant federal agencies and other entities (including AHRQ, CMS, DoD, National Library of Medicine (NLM), ONC, and VHA), accountable care organizations; state Medicaid programs; integrated health care systems; private payers; private agencies and software experts developing electronic medical records and other relevant programs, health service researchers; primary care and specialty clinicians; private payers, professional organizations; health care quality organizations (including the National Quality Forum); pain advocacy organizations; and people with pain.

Metrics: proportion of payments under the demonstrations that successfully support integrated care data; development of quality measures for integrated pain care, outcomes of care, including patient and family assessments, and impact on costs (for the demonstrations).

²⁹ An example would be episode groupers, which are software programs that organize claims data into clinically coherent episodes based, typically, on diagnosis. As designed for use by the Centers for Medicare and Medicaid Services and other payers, they help in identifying high-cost providers and also could be used for reimbursement purposes, much as diagnosis-related groups have been used in hospital reimbursement.

Professional Education and Training

Pain is one of the most common reasons for health care visits. Nonetheless, most professional health care education programs devote little time to education and training about pain and pain care. Given “strong indications that pain receives insufficient attention in virtually all phases of medical education,” the IOM report found “[e]ducation is a central part of the necessary cultural transformation of the approach to pain” and recommended improvement in the curriculum and education for health care professionals.³⁰

To assure the needed improvement, education and training must allow learners to achieve discipline-specific core competencies, which include empathy and cultural sensitivity, across a broad range of disciplines and prepare them to provide high quality team-based care for pain. Demonstration of competency in pain assessment, safe and effective pain care, and the risks associated with prescription analgesics should be a requirement for licensure and certification of health professionals and should be considered in curriculum review for accreditation of health professional training programs. These training enhancements should be developed in collaboration with relevant accrediting bodies and certifying boards to promulgate their use. Sub-specialty training and certification should include training in effective team management for patients with the most complex pain conditions.

The Problem: The high prevalence of pain across the population and its impact on individuals and families creates a significant responsibility for health care professionals. Despite the need to address this public health problem, many health professionals, especially physicians, are not adequately prepared and require greater knowledge and skills to contribute to the cultural transformation in the perception and treatment of people with pain. Education and training of health professionals in the complex etiology, prevention, assessment, safe and effective treatment of pain, and risks associated with poor pain management is insufficient, in part because educators lack access to valid information about pain and pain care. Core competencies in pain care are not fully developed and generally do not inform undergraduate (pre-licensure) curricula in health professions schools or graduate training programs, even those in pain medicine. As a result, practitioners may rely primarily on procedural or pharmacological approaches that alone are not effective and may have significant unintended adverse consequences such as addiction and medication misuse for which many health care providers lack skills and knowledge to identify and manage.

³⁰ IOM, 2011, p. 191, Finding 4-1, and Recommendation 4-2.

Moreover, cultural bias exists in the medical community against people with pain, especially those with chronic pain, which can negatively affect patient care and reinforce pain stigma. This bias and the documented decline in empathy as medical training progresses³¹ may be interrelated, in the case of pain care, and exacerbated by knowledge deficits, frustration with the limited effectiveness of usual treatments for chronic pain, and the complex nature of pain and pain care.

The intent of the professional education and training component of the National Pain Strategy is to anchor an attitudinal transformation toward pain and a reorganization of pain management by the health care system, in the education and training of health professionals. The mission includes grounding the pain-related education and training of physicians, nurses, clinical pharmacists, dentists, clinical health psychologists, physician's assistants, nurse practitioners, and other health professionals in core competencies, and making available easily accessible, evidence based information for educators to work toward this goal.

Objective 1: Develop, review, promulgate, and regularly update core competencies for pain care education and licensure and certification at the undergraduate and graduate levels.

Short-term strategies and deliverables:

- Convene an expert group that includes all relevant undergraduate health professions to review, revise, and promote the set of interdisciplinary core competencies that have been developed for undergraduate education in pain and pain care (Appendix J). The expert group should devise plans to incorporate the competencies into their programs, beginning with selected sites for piloting curricular changes. The relevant accrediting, certification, and licensing entities should be involved at early planning and subsequent phases of this strategy.
- Examine subspecialty training and certification in pain medicine through the planned effort of the Accreditation Council for Graduate Medical Education (ACGME), to assure that pain specialists are effectively trained to lead clinical teams in managing the most complex and challenging patients with acute and chronic pain and to provide needed support for formal and informal clinical medical education. Enhance team management training in currently existing ACGME- accredited programs (e.g. ACGME pain medicine residency requirements). Extend this examination to include nursing,

³¹ Neumann, M., F. Edelhäuser, D. Tauschel, M.R. Fischer, M. Wirtz, C. Woopen, A. Haramati, and C. Scheffer. 2011. Empathy decline and its reasons: A systematic review of studies with medical students and residents. *Acad Med* 86(8): 996-1009.

clinical pharmacy, clinical health psychology, and other relevant health professional training schools and programs.

- Solicit input from the public, including people with pain, professional organizations, and students, to enhance clinical empathy, cultural competency, and expanded patient-centered communication for people with pain, based on impact, feasibility, and ease of dissemination.

Medium-term strategies and deliverables:

- Promulgate interdisciplinary core competencies for undergraduate education for use in professional licensure examinations and educational accreditation standards.
- Convene an expert group from pain-relevant primary care specialties, including internal medicine, family medicine, pediatrics, obstetrics/gynecology to develop and promote core primary care competencies by building on the interdisciplinary core competencies and to approach ACGME regarding incorporation into relevant ACGME program requirements; participation from equivalent groups and accreditation boards in advanced practice nursing and physician assistant fields should be integrated into this process.
- Convene accrediting (e.g. ACGME, LCME) and certifying organizations and related groups to develop consensus and an implementation plan on the depth with which competency in pain care is integrated into health professions education, accreditation, and certification.
- Develop empathy-enhancing projects based on the solicited input.

Medium- and longer-term strategies and deliverables:

- Publish and promulgate core competencies in graduate education and training in primary care, through a work group convened for this purpose and in collaboration with relevant accrediting bodies.
- Develop and review, promote, and publish core competencies in pain care in relevant specialties, replicating the same general process used in primary care.
- Commission a baseline evaluation of the use of core competencies in undergraduate, graduate primary care and graduate specialty education and training, evaluate them over time to determine progress, and regularly update them.
- Evaluate the projects for enhancing empathy to determine their suitability for widespread use, and implement them accordingly.

Stakeholders and collaborators: CDC, FDA, Substance Abuse and Mental Health Service Administration (SAMHSA), and VHA, in collaboration with HRSA (as appropriate to their statutory priorities and within their authority) and other relevant federal agencies, and accreditation, certification, and licensing entities, including ACGME and Residency Review Committees, Association of American Medical Colleges, Liaison Committee on Medical Education, American Board of Medical Specialties, American Osteopathic Association, Coalition for Physician Accountability, Commission on Collegiate Nursing Education, Accreditation Commission for Education in Nursing, the Department of Education, the United Council for Neurological Subspecialties, selected specialty accreditation and certification bodies for physicians and nurses, related professional associations, equivalent groups in dentistry, clinical pharmacy, physical therapy, physician assistants, clinical health psychology and other relevant health

professions); pain advocacy organizations, and opioid use disorder advocacy organizations; and people with pain.

Coordinate with ongoing activities across HHS (including FDA, SAMHSA) on health care provider prescriber knowledge and skills for safe prescribing practices and identification of risks for opioid use disorder.

Metrics: validity and reliability of core competencies.

Objective 2: Develop a pain education portal that contains a comprehensive array of standardized materials to enhance available curricular and competency tools. The portal will serve as a central, comprehensive source for pain education materials and will be monitored regularly and updated as new evidence-based guidelines and resources are available. The need for knowledge and skills that address how clinician empathy influences the effectiveness of care should be included in the available educational materials.

Short-term strategies and deliverables:

- Convene expert stakeholders to survey current resources, link to other relevant electronic artifact portals, and determine the content for a pain education portal. The portal would contain evidence-based and/or peer reviewed best practices material about pain care and pain for use by educators and learners.
- Develop and evaluate a pilot portal that leverages the NIH Pain Consortium Centers of Excellence in Pain Education Coordination Center contract.

Medium-term strategies and deliverables:

- Launch the portal.
- Reconvene stakeholders to develop an annual survey to measure individual school's progress in teaching about pain. Systematic reviews of studies about pain education would be a starting point in developing the content of the survey.
- Conduct the initial survey of schools.

Longer-term strategies and deliverables:

- Monitor and keep updating the portal, which would be fully developed over a five-year horizon.
- Repeat the survey of schools and otherwise monitor pain education to assure that core competencies are taught.

Stakeholders and collaborators: AHRQ, CDC, FDA, NLM, ONC, SAMSHA, and other entities (including the DoD and VHA) (to leverage current resources, e.g. AHRQ's; United States Health Knowledge Information Data Base) develop content and architecture and strategies to monitor and promote the portal); professional organizations, and educators (to help develop survey and portal content); pain advocacy organizations; and people with pain.

Coordinate with resources developed across HHS, including FDA, SAMHSA, on health care provider prescriber educational resources for safe prescribing practices and identification of risks and care for opioid use disorder.

Metrics: Results of the annual survey of schools, to be promptly reported; use of the portal (such as frequency of access and downloading of materials) and user ratings; use of the survey results.

Public Education and Communication

The Institute of Medicine considered education central to a cultural transformation in pain care and recommended expanded and redesigned programs aimed at increasing public and patient understanding of pain. A national pain awareness campaign could draw on the experience of numerous federal agencies that have managed communications campaigns about public health topics as diverse as childhood immunizations, tobacco control, HIV/AIDS, depression, and nutrition.

Such campaigns generally involve numerous public and private partner organizations, each able to reach different segments of the population, use multiple media (including entertainment and social media), and require careful planning, research on audience segments' attitudes and beliefs and receptivity to test messages, and evaluation. A campaign with multiple components, heavy media buys, and other activities can be quite costly, which underscores the importance of focus and solid strategy development.

The National Pain Strategy envisions a significant effort to increase public awareness about pain and recommends two campaigns.³² The priority campaign is an extensive public awareness campaign about pain, and the secondary campaign would promote safe medication use by patients. Both should integrate health literacy principles and cross-cultural awareness and be tailored to specific audiences segmented by health status, demographic and cultural characteristics, and preferred informational media. These campaigns should be undertaken in such a way that they do not compete.

³² In general, the planning and implementation for the campaigns follow the stages outlined in the National Cancer Institute's Making Health Communication Programs Work (<http://www.cancer.gov/cancertopics/cancerlibrary/pinkbook/page1>).

The Problem: Pervasive stigma and misperceptions about pain are a root cause of significant and costly barriers to treatment and make it difficult for people with chronic pain to live productively and with dignity. Education is key to unlocking a necessary cultural transformation in the understanding of chronic pain, its care and treatment. In part, these problems arise because of the lack of high-quality, evidence-based communications campaigns that:

- Increase public awareness and knowledge about the pervasiveness of chronic pain, its complexity, and the importance of access to prompt and effective treatments
- Change cultural attitudes about chronic pain, debunking stereotypes and myths related to people with chronic pain and various pain treatment options and emphasizing the value of pain self-management programs in enabling people to live better with chronic pain
- Foster coalitions involving federal agencies, health care professionals and institutions, training and accreditation agencies, insurers, employers, foundations, patient advocate organizations, and others to participate in such campaigns and promote core messages, and
- Provide provider, public and patient education on the safe use of pain medications, including awareness of the risks for opioid misuse disorders that are associated with prescription pain medications.

The intent of the public education and communication component of the National Pain Strategy is to assure that chronic pain is recognized as a serious public health issue in the United States and that people with chronic pain have timely access to appropriate, safe pain care

Objective 1: Develop and implement a national public awareness and information campaign about the impact and seriousness of chronic pain, in order to counter stigma and correct common misperceptions.

Short-term strategies and deliverables:

- Select a broadly representative advisory panel of stakeholders, to include patients with pain and members of their families, advocacy groups, professional societies, policy groups, and others, as described below.
- Define campaign objectives, including intended audiences, advisory structure, and budget (potential learning objectives are in Appendix K).
- Develop requests for proposals for strategic communications firms to develop and conduct the campaign, review proposals, and select a firm (a separate firm may be engaged to conduct the evaluation).
- The selected firm would, as needed:
 - review available psychographic information regarding attitudes about pain (in the general population, in population subsets of interest, and in key stakeholder groups) and commission additional research, including surveys
 - review available evidence about settings, channels, and activities best suited to reach these audiences, and commission additional research
 - review existing information and educational materials
 - develop a communications strategy for each targeted audience, and

- work with the advisory board to identify and recruit partner organizations and define their roles in the campaign.
- Based on this preliminary work, develop and pretest messages and materials, using, wherever possible, information developed by other components of the National Pain Strategy

Medium-term strategies and deliverables

- Implement the program, including partner participation strategies, spokesperson training, and program-related services (e.g., pain self-management programs suggested in the Prevention and Care section), media (news, entertainment, social) strategies, and promotional materials.
- Monitor audience reach and feedback and partner engagement; adjust strategies as necessary.

Longer-term strategies and deliverables

- Conduct an outcome evaluation to assess campaign effectiveness, as measured by changes in public opinion related to the campaign’s learning objectives (e.g., the percent who agree “chronic pain is a disease”).
- Prepare a report based on the campaign evaluations for submission to a peer-reviewed scientific journal.
- As funds are available, continue to implement, assess, and adapt campaign components, as needed, and report on campaign outcomes in a peer-reviewed journal.

Stakeholders and collaborators: relevant federal agencies; public health organizations; professional organizations; insurers; human resources professionals; clinicians; patient advocacy organizations; and people with pain.

Metrics: the outcome evaluations would provide current data on public attitudes and those of relevant demographic or other subgroups.

Objective 2: Develop and implement a national educational campaign encouraging safe medication use, especially opioid use, among patients with pain.

Short-term strategies and deliverables:

- Identify an HHS team and select an advisory board with broad representation, including people with pain, as well as experts in health communications and public relations, to develop, plan, implement, and evaluate the campaign. The selected team would:
 - define the advisory structure and budget
 - review existing information and educational materials
 - review available research on attitudes, knowledge, and medication practices of patients with chronic pain who take opioid medications
 - review available evidence about settings, channels, and activities best suited to reach these patients, and commission additional research, as needed
 - develop a communications strategy, and

- identify and recruit partner organizations.
- Align campaign messages and approaches with ongoing HHS efforts to promote safe and appropriate use of prescription medications, such as electronic prescribing of controlled substances (EPCS).
- The campaign should cover the learning objectives and outcomes outlined in Appendix L.
- Based on this preliminary work, develop and pretest messages and materials.

Medium-term strategies and deliverables

- Implement the program, including partner participation strategies, spokesperson training, program-related services (e.g., a hotline), media (news, entertainment, social) strategies, and promotional materials.
- Monitor campaign reach and feedback and partner engagement; adjust strategies as necessary.

Longer-term strategies and deliverables

- Conduct an outcome evaluation through nationally representative surveys and when appropriate through pre- and post-test surveys, using outcome measures tailored to the learning objectives to assess campaign effectiveness.
- Conduct a five- to 10-year progress assessment of the issue of safe use of pain medications.
- Prepare reports based on the campaign evaluations for submission to a peer-reviewed scientific journal.
- Continue to implement, assess, and adapt campaign components, as needed, and report on campaign outcomes in a peer-reviewed journal.

Stakeholders and collaborators: relevant federal agencies/offices, including FDA, ODPHP, SAMHSA, public health organizations; professional organizations; insurers; human resources professionals; clinicians; credentialing bodies (e.g., the Federation of State Medical Boards), major retail pharmacy chains, the National Association of Boards of Pharmacy, professional pharmacy organizations and pharmacists; pain patient advocacy organizations and addiction and abuse advocacy organizations; and people with pain.

Metrics: the outcome evaluations would provide current data on the medication practices of patients with pain, which ideally could be compared with baseline data to determine any short-term trends.

APPENDIXES

- A. List of oversight panel members
- B. List of working group members, expert consultants, and staff
- C. Member nomination process and conflict of interest disclosure
- D. Chronic pain screener questions
- E. Operational questions for determining high-impact chronic pain
- F. Diagnostic clusters for population pain research
- G. Pain treatment indicators: Health care services for pain measurable with electronic health care data
- H. Public and private payer coverage and reimbursement methodologies for pain-related treatments
- I. The Stepped Care Model of pain care
- J. Core competencies for pain education
- K. Public education general campaign learning objectives
- L. Learning objectives and potential outcome measures for an educational campaign on safe use of pain medications

Appendix A. List of Oversight Panel Members

Sean C. Mackey, MD, PhD – Co-Chair

Chief, Division of Pain Medicine

Redlich Professor of Anesthesiology, Perioperative and Pain Medicine; Neurosciences; and Neurology (by courtesy)

Stanford University School of Medicine

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Appendix C. Member nomination process and conflict of interest disclosure

The National Pain Strategy (NPS) is a nationwide plan to address the core recommendations of the Institute of Medicine's (IOM) report, [Relieving Pain in America](#), on pain prevention, treatment, management, education, and research. The entity charged by HHS to address the IOM recommendations is the Interagency Pain Research Coordinating Committee (IPRCC), which was established under the Patient Protections and Affordable Care Act and, as such, is subject to rules and guidelines of the Federal Advisory Committee Act (FACA). The IPRCC's Task Force of experts, established to develop the NPS plan, also falls under the FACA rules and guidelines.

The Task Force is organized into six thematic working groups and an oversight panel and comprises approximately 80 members, with broad representation and expertise in accord with the recommendations of the IOM committee. Screening and selection of the NPS Task Force members was a multi-step process, performed according to FACA's requirements. A call for nominations was made through distribution to advocacy groups, professional societies, website notification, and email distribution. It was published as a Federal Register Notice as well. Candidates were selected based on expertise and knowledge, and the overall Task Force representation fulfilled IOM recommendations. A working group of the IPRCC screened and approved the slate of working group members.

Nominees were informed of the nature of conflicts of interests that would preclude their service and were required to disclose any potential conflicts and the nature of the conflicts. They were also required to disclose whether they were registered lobbyists, which precludes service under FACA. Conflict of interest disclosures were reviewed by the FACA Committee Management Officer and the IPRCC's Designated Federal Officer. If potential conflicts were identified, the nominee's conflict situation was reviewed by the NINDS Deputy Ethics Counselor to determine eligibility for service on the working group.

The working groups were advised of the needs and guidelines to protect the confidentiality of discussions to develop the NPS. Requests from all outside entities to present or provide unsolicited information to the working groups during the process were directed to the IPRCC's Designated Federal Officer.

Appendix D. Chronic pain screener questions

Definition	Item	Criteria												
Pain on at least half the days for 6 months	<p>Over the last six months, on about how many days have you had pain?</p> <p><input type="checkbox"/> I have not had pain</p> <p><input type="checkbox"/> I have had pain, but on less than half the days</p> <p><input type="checkbox"/> I have had pain on more than half the days, but not every day</p> <p><input type="checkbox"/> I have had pain every day, but not all the time</p> <p><input type="checkbox"/> I have had pain all day, every day, without break</p>	Chronic pain is pain on at least half the days over the past six months.												
Chronic pain severity (mild, moderate, severe)	<p>In the past 7 days, how would you rate your pain on average?</p> <p>0=No pain 10= Worst imaginable pain</p> <p>In the past 7 days, how much did pain interfere with <u>your day-to-day activities</u>?</p> <p>0=No interference 10=Completely interferes</p> <p>In the past 7 days, how much did pain interfere with <u>your enjoyment of life</u>?</p> <p>0=No interference 10=Completely interferes</p>	<p>Mean or sum of the three 0-10 pain ratings.</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th style="text-align: center;"><u>Mean</u></th> <th style="text-align: center;"><u>Sum</u></th> </tr> </thead> <tbody> <tr> <td>Mild</td> <td style="text-align: center;">< 4</td> <td style="text-align: center;">< 12</td> </tr> <tr> <td>Moderate</td> <td style="text-align: center;">4 to < 7</td> <td style="text-align: center;">12 to 20</td> </tr> <tr> <td>Severe</td> <td style="text-align: center;">7 to 10</td> <td style="text-align: center;">21 to 30</td> </tr> </tbody> </table> <p>NOTE: If only two pain ratings are available, divide by the sum by two and multiple by 3 to obtain an estimated sum score.</p>		<u>Mean</u>	<u>Sum</u>	Mild	< 4	< 12	Moderate	4 to < 7	12 to 20	Severe	7 to 10	21 to 30
	<u>Mean</u>	<u>Sum</u>												
Mild	< 4	< 12												
Moderate	4 to < 7	12 to 20												
Severe	7 to 10	21 to 30												

Appendix E. Operational questions for determining high-impact chronic pain

Among people with chronic pain (as determined by screener questions in Appendix D), high-impact chronic pain is operationally defined by enduring participation restrictions because of pain, including:

<p>Participation restrictions because of pain</p>	<p><i>Over the past 6 months because of pain...</i></p> <p>I have had trouble doing my usual work (including work for pay, work around the home, volunteer work).</p> <p>Never Rarely Sometimes Usually Always</p> <p>I have had trouble doing my regular social and recreational activities (such as visiting friends, going to the movies, attending clubs or religious activities).</p> <p>Never Rarely Sometimes Usually Always</p> <p>I have had trouble taking care of myself (for example dressing, bathing, or feeding myself).</p> <p>Never Rarely Sometimes Usually Always</p>	<p>At least one item rated “usually” or “always”</p>
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Appendix F. Diagnostic clusters for population pain research

1. Back pain
2. Neck pain
3. Limb/extremity pain, arthritis disorders (including osteoarthritis and joint pain)
4. Fibromyalgia and wide-spread muscle pain
5. Headache
6. Orofacial, ear, and temporomandibular disorder pain
7. Abdominal pain and bowel pain
8. Chest pain
9. Urogenital, pelvic, and menstrual pain
10. Fractures, contusions, sprains and strains
11. Other painful conditions. This includes sickle cell disease, complex regional pain syndrome, systemic lupus erythematosus, acquired deformities (excluding spinal disorders), spinal cord injury, Lyme disease, Neuropathic pain. Note: Cancer pain is included here, but relevant diagnostic codes need to be identified.

Appendix G. Pain treatment indicators: Health care services for pain measurable with electronic health care data

Type of service	Sub-types	Notes	Identification
Professional services	Primary care visits		Provider codes in combination with Diagnostic Clusters.
	Pain specialist visits	Differentiate type of specialist (e.g. neurology, orthopedic surgery, rehabilitation medicine, anesthesiology, rheumatology)	
	Physical therapy visits		
	Occupational therapy visits		
	Psychologist visits		
	Chiropractic visits	These may not be routinely available in many electronic health care databases.	
	Alternative/complementary care visits		
Oral medications	Opioids	Differentiate short-acting and extended release. Chronic use may be defined by 70+ days supply in a 90 day period, receiving 6+ dispensings in a year, or other indication of sustained use.	National Drug Classification (NDC codes) in combination with Diagnostic Clusters when necessary
	NSAIDS	Only available when prescribed, not over-the-counter.	
	Sedatives, anti-anxiety agents, sleep medications and muscle relaxants	Chronic use may be defined by 45+ days supply in a 90 day period or other indication of sustained, frequent use.	
	Tryptans		
	Anticonvulsants		
	Antidepressants	SSRI, SNRI, Tricyclic antidepressants and other heterocyclic medications may be differentiated.	

	Aspirin and acetaminophen	These will not be adequately captured by electronic health care data because they are generally taken over-the-counter	
Procedures	Surgery	Differentiate anatomical site of surgery (back, hip, knee, shoulder, etc.) and type of surgery within anatomical site (e.g. laminectomy, fusion, discectomy for back surgery).	Procedure codes in combination with Diagnostic Clusters when necessary
	Injections, blocks and infusions	Differentiate type (e.g., epidural steroid injections, selective nerve root blocks, trigger point injections, facet point injections, sympathetic nerve root blocks, joint injections, peripheral nerve blocks).	
	TENS, spinal cord stimulation, deep brain stimulation		
Inpatient care	Surgical admission		
	Non-surgical admission		Diagnostic codes identifying primary reason for admission

Appendix H. Public and private payer coverage and reimbursement methodologies for pain-related treatments

Public & Private Payer Coverage of Pain-Related Treatments						
Payor	Pain-related Treatments					
	Medications	Regional Anesthetic Interventions	Surgery	Psychological Therapies	Rehabilitative/Physical Therapy	Complementary and Alternative Medicines (CAM)
Medicaid	X	No state specific data found	X	X	X	X ⁵
Medicare	X	X	X	X ³	X ⁴	X ⁵
Private Insurers (BCBSM example)	X	X	X	X	X	X
Veterans Health Administration (VHA)	X	X	X	X	X	X ⁶
U.S. Department of Defense (DoD)/ TRICARE ¹	X	X	X	X	X	X ⁷
Federal and State Workers'	State: X Federal: X	State: X Federal: X	State: X Federal: X	State: No state specific data found	State: X Federal: X	State: No state specific data found

Compensation Programs²				<i>Federal: X</i>		<i>Federal: X</i>
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“X” indicates the payer offers coverage for procedure(s) within the treatment category

¹ TRICARE is the health care program of the DoD Military Health System and is administered through managed care support contracts. The program offers service members and their families three main health plan options (TRICARE Prime, TRICARE Standard, and TRICARE Extra) that allow them to receive care from private health care providers.

² The Federal Employees’ Compensation Act (FECA) is the workers’ compensation program for federal employees and provides medical benefits to employees who are injured or become ill in the course of their federal employment. FECA covers all medical costs associated with the treatment of the work-related injury or illness. FECA benefits are paid out of the congressionally appropriated Federal Employees’ Compensation Fund. In contrast, state workers’ compensation programs are regulated by the state and provided through private insurance, state insurance funds, or self-insurance. Policies and programs vary widely among states.

³ In 2014, Medicare beneficiaries will be responsible for paying a 20% coinsurance for outpatient psychological counseling services. In previous years the coinsurance was 35-40 percent.

⁴ Most health plans have limitations on physical therapy and occupational therapy services. For 2014, Medicare has a \$1,920 annual cap for physical and speech therapy and a \$1,920 annual cap for rehabilitative services. Many Medicare Advantage plans have chosen not to institute a therapy cap.

⁵ Medicare and Medicaid: Medicare and most state Medicaid programs only cover chiropractic services for manual manipulation of the spine to treat a subluxation (when one or more bones in the spine move out of position). A few state Medicaid programs, such as Florida and Rhode Island, have covered other CAM services, including acupuncture and massage therapy.

⁶ Every VHA provider has a specific requirement to make chiropractic services available onsite.

⁷ While some military medical facilities may offer services like acupuncture and chiropractic care, these are reserved for active duty members only. CAM services are largely excluded under TRICARE.

Sources: Kaiser Family Foundation, State Facts, Medicaid Benefits, 2011; Centers for Medicare & Medicaid Services; BCBSM; TRICARE; VHA; Department of Defense, Report to the Congress: Complementary and Alternative Medicine within the Military Health System, 2011; Department of Defense, Report to the Congress: The Implementation of a Comprehensive Policy On Pain Management by the Military Health Care System; Congressional Research Service, The Federal Employees’ Compensation Act (FECA): Workers’ Compensation for Federal Employees, June 2013.

Public & Private Reimbursement Methodologies for Pain-Related Treatments

Payor ¹	Pain-related Treatments					
	Medications	Regional Anesthetic Interventions	Surgery	Psychological Therapies	Rehabilitative/Physical Therapy	Complementary and Alternative Medicines (CAM)
Medicaid²	States use varied methods. Most estimate the acquisition cost for a prescription drug and add a dispensing fee.	No state specific data found	Varies by state	35 states use fee-for-service to reimburse for psychologist services for individuals enrolled in adult Medicaid.	33 states use fee-for-service to reimburse for occupational therapy services for individuals enrolled in adult Medicaid. 35 states and DC states use fee-for-service to reimburse for physical therapy services for individuals enrolled in adult Medicaid.	26 states use fee-for services to reimburse for chiropractic services for individuals enrolled in adult Medicaid.
Medicare	Medicare Part D sponsors negotiate prices with pharmacies and manufacturers. The negotiated price includes the ingredient cost and dispensing fee.	Fee-for-Service	Fee-for-Service and Prospective Payment System	Fee-for-Service	Fee-for-Service (Outpatient Facility) and Prospective Payment System (Inpatient and Nursing Facility)	Fee-for-Service
Private Insurers (BCBSM example)	Fee-for-Service	Fee-for-Service	Fee-for-Service	Fee-for-Service	Fee-for-Service	Fee-for-Service

Veterans Health Administration (VHA) ³	VA negotiates pricing and purchases directly from wholesalers and manufacturers.	Global Budget	Global Budget	Global Budget	Global Budget	Global Budget
U.S. Department of Defense (DoD)/ TRICARE ⁴	DoD negotiates prices with pharmacies and manufacturers.	Fee-for-Service	Fee-for-Service and Prospective Payment System	Fee-for-Service	Fee-for-Service and Prospective Payment System	Fee-for-Service
Federal and State Workers' Compensation Programs ⁵	<i>State:</i> Varies by state <i>Federal:</i> Based on the Average Wholesale Price (AWP) for prescription drugs plus a dispensing fee, or on the Usual and Customary charge amount (whichever is less).	<i>State:</i> Fee-for-Service <i>Federal:</i> Fee-for-Service	<i>State:</i> Varies by state <i>Federal:</i> Fee-for-Service and Prospective Payment System	<i>State:</i> Fee-for-Service <i>Federal:</i> Fee-for-Service	<i>State:</i> Varies by state <i>Federal:</i> Fee-for-Service and Prospective Payment System	<i>State:</i> Fee-for-Service <i>Federal:</i> Fee-for-Service

¹ All payers appear to be relying largely on single modality approaches.

² In July 2011, almost 75% of Medicaid beneficiaries were enrolled in a managed care program. Benefits that are not included in a state's managed care contract are often provided on a fee-for-service basis or by a non-comprehensive prepaid health plan.

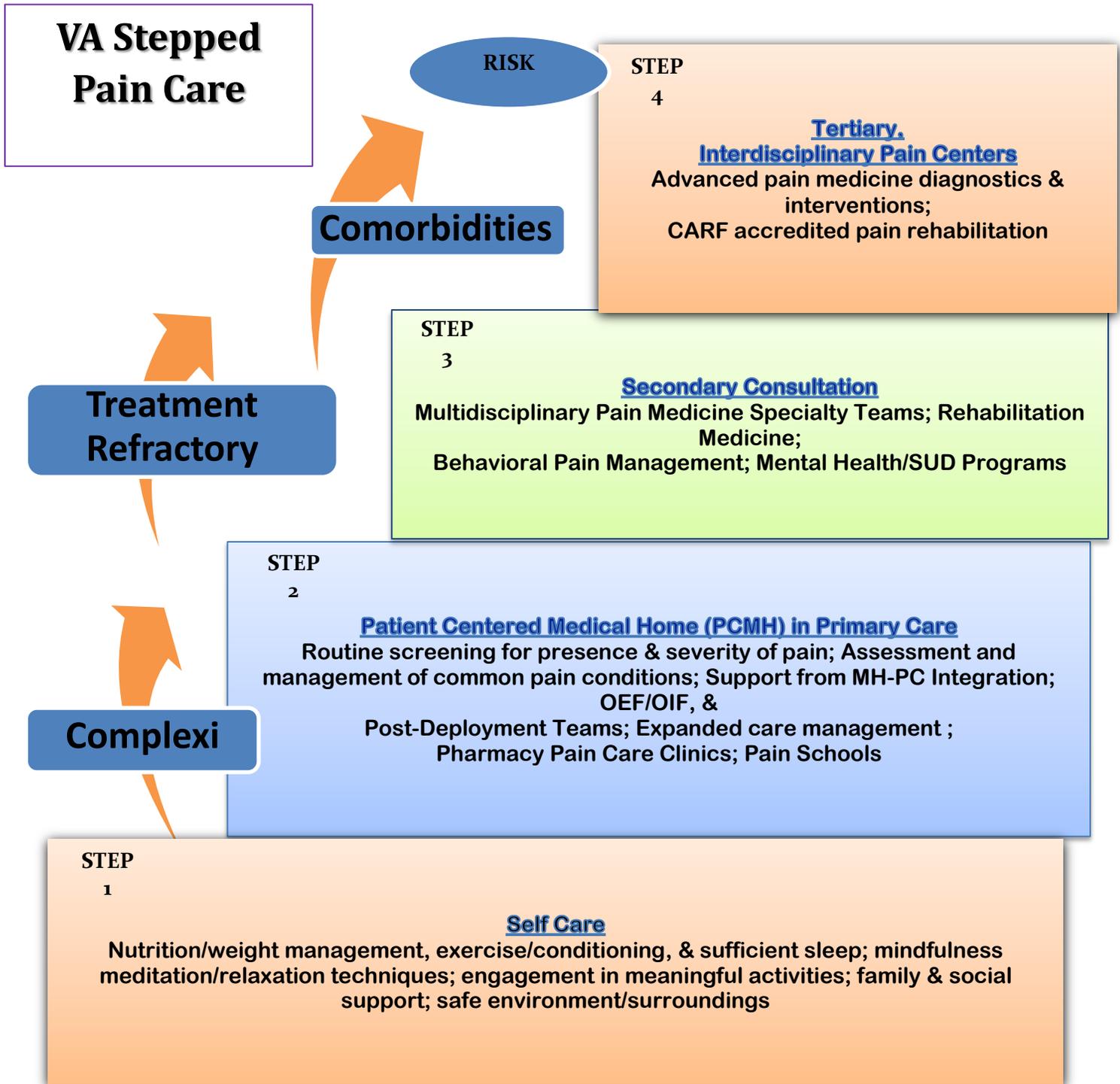
³ The VHA, within the Department of Veterans Affairs, is appropriated a fixed amount of funds by Congress. Those funds are distributed to 23 regional service networks. The amount distributed to each region is determined by the Veterans Equitable Resource Allocation (VERA) system, an allocation method based on the number of patients served in the region and the severity of their conditions. VHA facilities do bill third-party payers (e.g., private insurance) for nonservice-connected care. The funds generated from third-party payers go to the billing VHA facility. The VHA does reimburse for care provided at non-VHA facilities, using fee-for-service, when a veteran is unable to access care at a VHA facility in emergencies, if a covered service cannot be provided at a VHA facility, or due to geographic inaccessibility.

⁴ Reimbursement rates for TRICARE are generally aligned with Medicare. Health care providers who are employed at military medical facilities are salaried, like the VHA, and do not receive reimbursements from TRICARE for the care they provide.

⁵ Reimbursement rates for the services covered by FECA are determined by the Department of Labor's Office of Workers' Compensation Programs fee schedule, which are generally aligned with Medicare. Similar to FECA, fee-for-service is the most common payment method among state workers' compensation programs. Payments made under state programs are generally greater than Medicare payments.

Sources: Kaiser Family Foundation, State Facts, Medicaid Benefits, 2011; Centers for Medicare & Medicaid Services; BCBSM; Congressional Research Service, Military Medical Care: Questions and Answers, January 2014; Congressional Research Service, Health Care for Veterans: Answers to Frequently Asked Questions, February 2014; Government Accountability Office, Access to Civilian Providers under TRICARE Standard and Extra, June 2011; U.S. Department of Labor, OWCP Medical Fee Schedule 2013.

Appendix I. The VA Stepped Care Model of pain care



Appendix J. Core competencies for pain education

Core competencies for pain management from an inter-professional consensus summit have been endorsed widely and supported by national healthcare organizations across the major health professions. These may serve as a starting point for accrediting and credentialing organizations to help guide educators to develop and revise curriculum that advances care for effectively preventing and managing pain.

Box 1 Pain management domains and core competencies

Domain one

Multidimensional nature of pain: What is pain?

This domain focuses on the fundamental concepts of pain including the science, nomenclature, and experience of pain, and pain's impact on the individual and society.

1. Explain the complex, multidimensional, and individual-specific nature of pain.
2. Present theories and science for understanding pain.
3. Define terminology for describing pain and associated conditions.
4. Describe the impact of pain on society.
5. Explain how cultural, institutional, societal, and regulatory influences affect assessment and management of pain.

Domain two

Pain assessment and measurement: How is pain recognized?

This domain relates to how pain is assessed, quantified, and communicated, in addition to how the individual, the health system, and society affect these activities.

1. Use valid and reliable tools for measuring pain and associated symptoms to assess and reassess related outcomes as appropriate for the clinical context and population.
2. Describe patient, provider, and system factors that can facilitate or interfere with effective pain assessment and management.
3. Assess patient preferences and values to determine pain-related goals and priorities.
4. Demonstrate empathic and compassionate communication during pain assessment.

Domain three

Management of pain: How is pain relieved?

This domain focuses on collaborative approaches to decision-making, diversity of treatment options, the importance of patient agency, risk management, flexibility in care, and treatment based on appropriate understanding of the clinical condition.

1. Demonstrate the inclusion of patient and others, as appropriate, in the education and shared decision-making process for pain care.
2. Identify pain treatment options that can be accessed in a comprehensive pain management plan.
3. Explain how health promotion and self-management strategies are important to the management of pain.
4. Develop a pain treatment plan based on benefits and risks of available treatments.
5. Monitor effects of pain management approaches to adjust the plan of care as needed.
6. Differentiate physical dependence, substance use disorder, misuse, tolerance, addiction, and nonadherence.
7. Develop a treatment plan that takes into account the differences between acute pain, acute-on-chronic pain, chronic/persistent pain, and pain at the end of life.

Domain four

Clinical conditions: How does context influence pain management?

This domain focuses on the role of the clinician in the application of the competencies developed in domains 1–3 and in the context of varied patient populations, settings, and care teams.

1. Describe the unique pain assessment and management needs of special populations.
2. Explain how to assess and manage pain across settings and transitions of care.
3. Describe the role, scope of practice, and contribution of the different professions within a pain management care team.
4. Implement an individualized pain management plan that integrates the perspectives of patients, their social support systems, and health care providers in the context of available resources.
5. Describe the role of the clinician as an advocate in assisting patients to meet treatment goals.

Appendix K. Public education general campaign learning objectives

To increase public awareness about pain and people with pain, the committee recommends developing a campaign that will cover the following learning objectives (listed in order of priority):

1. Chronic pain is a disease.
2. Chronic pain is manageable.
3. Chronic pain is more prevalent than cancer, diabetes, and heart disease combined.
4. Chronic pain is real.
5. Most Americans will experience chronic pain or care for someone with chronic pain.
6. People in chronic pain deserve respect, compassion, and access to timely treatment.
7. Many people in chronic pain nevertheless live productive lives.
8. Chronic pain may cause depression and depression increases the severity of pain.
9. Chronic pain may require a spectrum of medical treatments and/or non-medical interventions along with the active participation of people with chronic pain in their own pain care management.
10. Appropriate chronic pain management may involve prescription medications, which require knowledge of risks for adverse effects such as dependency and addiction.
11. Activity level and mood may vary depending on the intensity of chronic pain (good days and bad days).

Appendix L. Learning objectives and potential outcome measures for an educational campaign on safe use of pain medications

Learning Objectives

Increasing the number of people with chronic pain who report that they:

1. Talk with their clinician about their hopes and expectations and share activities of daily living or function that are important to them.
2. Work with their clinician to develop a plan of treatment consistent with their goals.
3. Know that analgesic medications can be an appropriate pain management option, but they are not the only option.
4. Know their prescription medication is only for them and do not share it with others.
5. Store their medicine in a safe place where children or pets cannot reach it.
6. Dispose of unused medication properly.
7. Take medicine only if it has been prescribed or approved by their doctor.
8. Do not take more medicine or take it more often than instructed. They call their doctor if their pain worsens.
9. Know how to understand and recognize expected and unexpected adverse effects such as dependency and addiction and to discuss risks with their doctor.
10. They talk to their doctor before taking prescription medications in combination with other drugs, including alcohol, sleeping pills, or anti-anxiety medication.
11. Have discussed with family and friends how to recognize and respond to overdose.

Potential Outcome Measures

Where possible, existing data sources should be employed to monitor measures such as:*

1. Proportion of patient who
 - a. discuss daily activities (quality of life) with their physician
 - b. discuss expectations about the outcomes of pain treatment and side effects with their physician
 - c. have a functional contract (defined) with their physician and discuss with their doctor appropriate alternative treatments (NSDUH)
2. Number of patients taking opioids who:
 - a. report storing their medication safely
 - b. do not save back medications (CPDA)
 - c. dispose of unused medication properly (CPDA)
 - d. take opioids not prescribed for them (NSDUH)
 - e. take higher doses or more frequent doses than prescribed (DAWN)
 - f. report calling their doctor if pain worsens
 - g. report mixing pain medicines with alcohol, sleeping pills, or any illicit substance (DAWN).
3. Number of overdoses reported in national emergency department data (DAWN).

*Potential data sources for some of these research questions are: the Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health (NSDUH) and Drug Abuse Warning Network (DAWN), and Research America's National Poll on Chronic Pain and Drug Addiction (CPDA).

Five Things Physicians and Patients Should Question

1

Don't prescribe opioid analgesics as first-line therapy to treat chronic non-cancer pain.

Physicians should consider multimodal therapy, including non-drug treatments such as behavioral and physical therapies prior to pharmacological intervention. If drug therapy appears indicated, non-opioid medication (e.g., NSAIDs, anticonvulsants, etc.) should be trialed prior to commencing opioids.

2

Don't prescribe opioid analgesics as long-term therapy to treat chronic non-cancer pain until the risks are considered and discussed with the patient.

Patients should be informed of the risks of such treatment, including the potential for addiction. Physicians and patients should review and sign a written agreement that identifies the responsibilities of each party (e.g., urine drug testing) and the consequences of non-compliance with the agreement. Physicians should be cautious in co-prescribing opioids and benzodiazepines. Physicians should proactively evaluate and treat, if indicated, the nearly universal side effects of constipation and low testosterone or estrogen.

3

Avoid imaging studies (MRI, CT or X-rays) for acute low back pain without specific indications.

Imaging for low back pain in the first six weeks after pain begins should be avoided in the absence of specific clinical indications (e.g., history of cancer with potential metastases, known aortic aneurysm, progressive neurologic deficit, etc.). Most low back pain does not need imaging and doing so may reveal incidental findings that divert attention and increase the risk of having unhelpful surgery.

4

Don't use intravenous sedation for diagnostic and therapeutic nerve blocks, or joint injections as a default practice.*

Intravenous sedation, such as with propofol, midazolam or ultrashort-acting opioid infusions for diagnostic and therapeutic nerve blocks, or joint injections, should not be used as the default practice. Ideally, diagnostic procedures should be performed with local anesthetic alone. Intravenous sedation can be used after evaluation and discussion of risks, including interference with assessing the acute pain relieving effects of the procedure and the potential for false positive responses. American Society of Anesthesiologists Standards for Basic Anesthetic Monitoring should be followed in cases where moderate or deep sedation is provided or anticipated.

5

Avoid irreversible interventions for non-cancer pain that carry significant costs and/or risks.

Irreversible interventions for non-cancer pain, such as peripheral chemical neurolytic blocks or peripheral radiofrequency ablation, should be avoided because they may carry significant long-term risks of weakness, numbness or increased pain.

*This recommendation does not apply to pediatric patients.

How This List Was Created

The American Society of Anesthesiologists (ASA) Committee on Pain Medicine was charged with developing the “Top 5 List” on pain medicine for the *Choosing Wisely*[®] campaign. Committee members submitted potential recommendations for the campaign, and from this list voted on which recommendations should be included in the final “Top 5 List.” The literature was then searched to provide supporting evidence. The Committee communicated electronically and met in person during the development and approval process. Once approved by the Committee, the “Top 5 List” was reviewed by ASA’s Chair of the Section on Subspecialties, Vice President for Scientific Affairs, Executive Committee and Administrative Council. ASA’s “Top 5 List” for pain medicine has been endorsed by the American Pain Society.

ASA’s disclosure and conflict of interest policy can be found at www.asahq.org.

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About the ABIM Foundation

The mission of the ABIM Foundation is to advance medical professionalism to improve the health care system. We achieve this by collaborating with physicians and physician leaders, medical trainees, health care delivery systems, payers, policymakers, consumer organizations and patients to foster a shared understanding of professionalism and how they can adopt the tenets of professionalism in practice.

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About the American Society of Anesthesiologists

The American Society of Anesthesiologists (ASA) is an educational research and scientific association of physicians organized to raise and maintain the standards of the medical practice of anesthesiology and improve the care of the patient. Since its founding in 1905, the Society’s achievements have made it an important voice in American medicine and the foremost advocate for all patients who require anesthesia or relief from pain. As physicians, anesthesiologists are responsible for administering anesthesia to relieve pain and for managing vital life functions, including breathing, heart rhythm and blood pressure, during surgery. After surgery, they maintain the patient in a comfortable state during the recovery and are involved in the provision of critical care medicine in the intensive care unit.

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Part XVI
**Rational Opioid Therapy for Cancer
and Noncancer Pain**

Adaptations to Continuous Opioid Use: The Role of Tolerance, Dependence, and Memory

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Educational Objectives

1. Outline the basic mechanisms of opioid tolerance and dependence.
2. Explain the reasons why opioid tolerance and dependence underlie opioid treatment failure.
3. Rationalize addiction definitions.

Introduction

That the dried juice of the opium poppy is capable of producing a state of oblivion in humans, thus relieving pain and suffering, has been known for millennia. It is only in the past few decades, however, that the neurobiological basis of these opioid actions has been understood. This knowledge throws enormous light on historic observations such as the propensity of opioids to produce addiction, the marked development of tolerance to opioid effects over time, the dimming of analgesic benefit over time, and the importance of context and environment in determining opioid actions. This chapter describes the neuroadaptations to continuous opioid use, in particular the neuroadaptations that produce tolerance, dependence, and the irreversible neurobiological state of addiction.

Tolerance and Dependence

The existence of an endogenous system of opioids and opioid receptors, a so-called “reward center” in

the limbic system of the brain, and bidirectional pain pathways in the spinal cord, thalamus, and higher centers, are all 20th-century discoveries that help in understanding opioid actions and the adaptations that arise when opioid drugs are used [5,9,20]. The mesocorticolimbic system (“reward center”) and pain pathways are replete with opioid receptors, and opioid receptors are also found in the respiratory center, in the gut, throughout the neuroendocrine system, and on immune cells, explaining many of the side effects of opioid therapy [15,17]. Because of their strong affinity for this endogenous and widespread system of receptors, opioid drugs show a strong propensity to produce tolerance—the need for more drug to produce the same effect over time. Many mechanisms have been suggested to explain opioid tolerance, including downregulation (a reduction in the turnover rate and number of opioid receptors), desensitization, or a combination [6,7,22]. In addition to these pharmacological mechanisms, tolerance can be produced by psychological factors, in which case it is termed “associative” or “learned” tolerance [14]. Changes in mood, for example, can change opioid tolerance, so that tolerance could change as a consequence of depression, or for addicts, when presented with contextual clues such as prior circumstances of drug use. Tolerance could change rapidly, as it might with a sudden change in circumstance such as admission to hospital, or it may change more insidiously over time, in which case the change in tolerance may not be obvious. Tolerance was

once considered to be the chief characteristic of addiction because it was observed that addicts seek higher and higher doses to maintain their habit. The existence or nonexistence of tolerance to opioids' analgesic effects, as distinct from tolerance to euphoria, is much debated. The reason for the debate is that there are patients whose established effective dose provides stable analgesia over months or even years, arguing against the existence of analgesic tolerance. There are others, however, who require dose escalation over time, which could be accounted for by associative or non-associative tolerance, or even by opioid-induced hyperalgesia.

Tolerance is the first important adaptation to continuous opioid use, the second being dependence. Dependence, so called, means that drug is not easily given up because unpleasant symptoms arise either when the drug is withdrawn, or when the dose becomes inadequate. The importance of the latter is that increases in tolerance that are not satisfied with increases in opioid dosing will produce symptoms of withdrawal that are unpleasant. Dependence thus becomes an important driver of opioid seeking [12,13] Opioid tolerance and dependence really are not separate phenomena, but are aligned—whatever changes there are in one will alter the other (Fig. 1). Together, tolerance and dependence are important adaptations to continuous opioid use, and they explain failed opioid therapy—the state whereby analgesia is not adequate and doses may have reached toxic levels, yet the symptoms

of withdrawal are so severe that the subject feels unable to wean from or discontinue opioid therapy [2,4].

Addiction

In the writing of addiction criteria by the American Psychiatric Association (*Diagnostic and Statistical Manual* [DSM]) [1] and the World Health Organization ICD coding [23], as well as in standard teaching about pain and addiction, a distinction is carefully made between “physical” and other types of dependence. The term “physical dependence” is used to denote dependence that results in classical “physical” withdrawal symptoms such as agitation, anxiety, nausea, sweating, and runny nose, which arise from dysregulation of central noradrenergic nuclei and are noradrenergic effects. However, withdrawal symptoms also include hyperalgesia (flu-like symptoms with general achiness), and anhedonia (a sense of let-down), symptoms that can be as distressing and intolerable as the symptoms of noradrenergic overdrive. Confusion arises because many people consider that hyperalgesia and anhedonia are embraced under the term “physical,” while others consider them distinctly psychological. Although it may seem attractive to bundle all withdrawal symptoms under the term “physical” [8,21], this becomes problematic when a common clinical observation is that classical “physical” withdrawal symptoms are relatively short-lived (days or

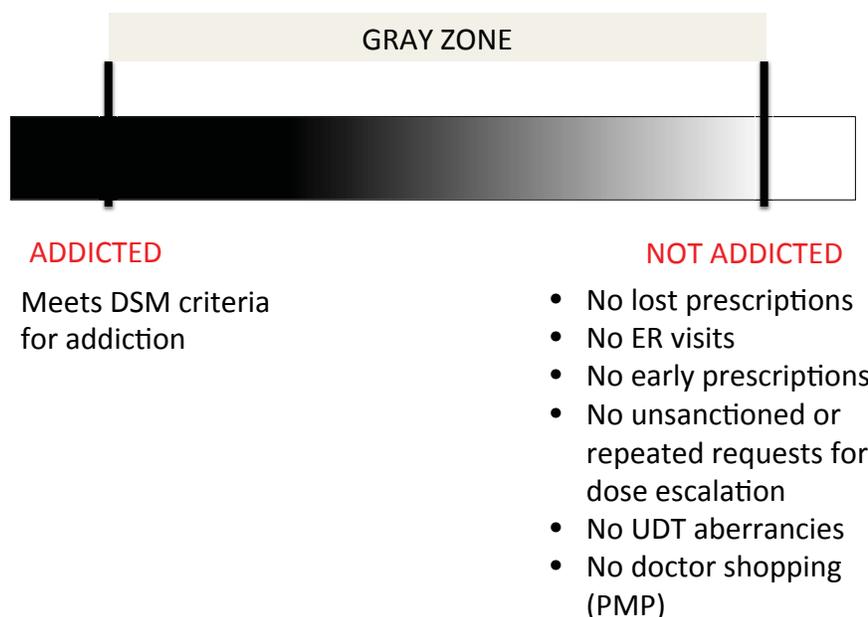


Fig. 1. Spectrum of dependence and addiction. ER, emergency room; PMP = prescription monitoring program (now available in several states in the United States, in continued development); UDT, urine drug test. Doctor shopping occurs in the United States because many patients have multiple providers, unlike countries with national health systems, where patients have a medical “home.”

weeks), whereas some of the other symptoms, particularly psychological symptoms, seem to last longer (months or years). But then is this irreversible or difficult-to-reverse state actually addiction and not dependence? It seems there is no clear answer to this question, largely because, despite the existence of criteria that aptly describe behaviors seen in the population of patients who become addicted through illicit use, criteria for addiction are not so easy to define in patients who become addicted through opioid pain treatment [4,19]. Table I presents DSM behavioral criteria for addiction on the left, and behaviors that arise in opioid-treated pain patients on the right [1,24]. The reader can see that the behaviors on the left may not be considered suggestive of addiction in pain patients because pain itself can cause these types of behavior,

today to be an irreversible neurobiological disease characterized by loss of control over drug use [16,18]. What takes the reversible state of dependence to the level of being irreversible? The irreversible state of addiction arises as a consequence of continued drug use combined with repeated drug-seeking behaviors. This state occurs in structures involved in memory, distinct from the mesocorticolimbic system, including the amygdala, hippocampus, prefrontal cortex, and thalamus. The process is one of conditioning, and like all conditioning, the more incessant the stimulation, the less easy it is to eradicate [10,11]. For the person who becomes addicted to illicit drugs, the behaviors that form the basis for the conditioning are all related to drug seeking. For the pain patient, the conditioning process is not as simple. Not only are the drug-seeking behaviors themselves of

Table I
Behavioral criteria for addiction (left) and behaviors that arise in opioid-treated pain patients (right)

Factors Suggesting Maladaptive Substance Use	Behaviors Suggesting Prescription Drug Abuse
A maladaptive pattern of substance use leading to clinically significant impairment or distress is manifested by two or more of the following:	Multiple prescribers
Failure to fulfill major role obligations at work, school or home	Frequent emergency room visits
Continue in situations in which it is physically hazardous (e.g., driving)	Multiple drug intolerances described as “allergies” and refusal to pursue nonopioid treatments
Persistent or recurrent social or interpersonal problems	Frequent dose escalations and self-dose escalation
Substance taken in larger amounts or longer than was intended	Frequent running out of medication early
Persistent desire or unsuccessful effort to cut down	Frequent telephone calls to clinic and early appointments
Great deal of time spent in activities necessary to obtain substance, use substance or recover from substance use	Focusing mainly on opioid issues during visits
Important social, occupations or recreational activities given up or reduced	Repeated prescription loss with “classic” excuses such as “The dog ate my prescription,” “The airline lost my baggage,” “The medicine was stolen”
Continued use despite knowledge of harm	
Craving	

Source: Behavioral criteria used for Substance Use Disorder, *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition [1]. Right-hand column is adapted from Wilsey and Fishman [24].

while the behaviors on the right are very different to those on the left. We have tremendous difficulty actually distinguishing and identifying patients who have developed addiction during opioid pain treatment, largely because of lack of consensus about what constitutes addictive behavior in patients receiving opioids for the treatment of pain [3]. To make matters worse, what we find in the clinical setting is a very large gray area into which most patients fall in the spectrum between clearly addicted versus clearly not addicted (Fig. 2).

One factor that seems critical in addiction definitions is its irreversibility. Drug addiction is understood

a different nature (see columns 1 versus 2, Table I), they are often not clearly distinguishable from relief seeking. To complicate the clinical picture even further, memories and conditioning for pain patients also incorporate memories of being in pain (a much-dreaded and anxiety-provoking state), and memories of obtaining pain relief when opioids were initiated (a much desired state). It is not even possible to tease apart conditioning related to pain, pain relief, and drug seeking, thus making it even more difficult to be clear about what exactly addiction is in opioid-treated pain patients. All the memories are related to drug seeking, and all are irreversible. The state of dependence or addiction in pain

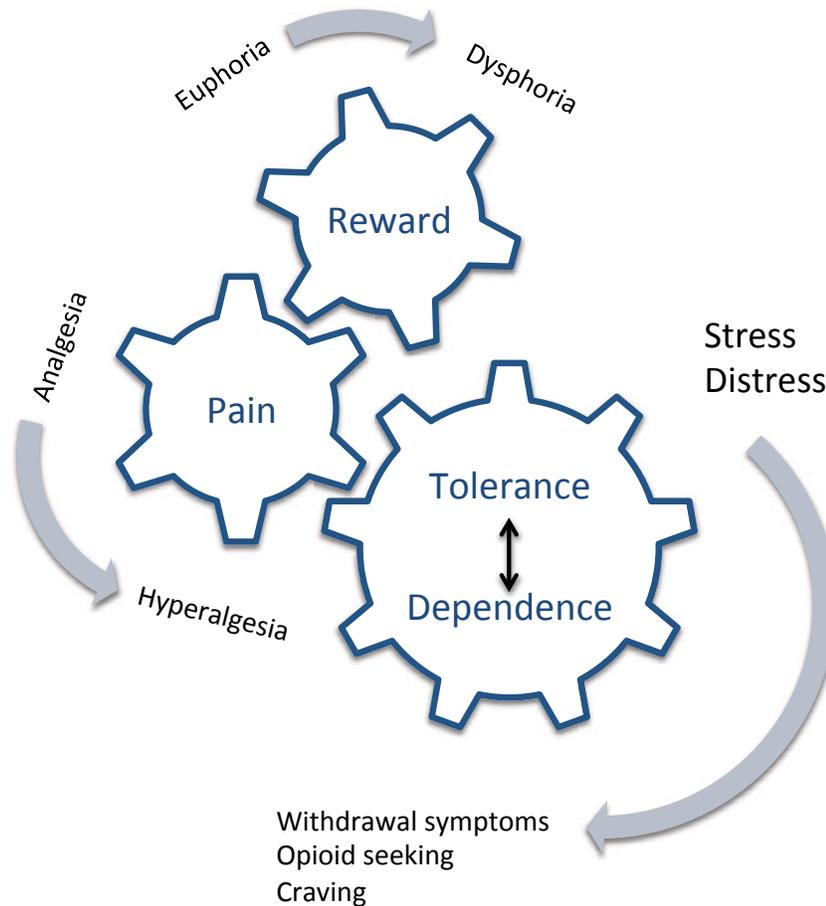


Fig. 2. Interdependence of mood, tolerance/dependence, and pain. Even in normal individuals, pain and mood are interdependent, in part through endogenous opioid mechanisms. Individuals taking exogenous opioids chronically and continuously adapt by developing tolerance and dependence. Psychological factors such as stress and distress can alter tolerance and thereby induce withdrawal symptoms. For the dependent individual, the need for more opioid becomes the predominant reaction to stress. Although pain is seen as the primary reason to dose-escalate, pain is often secondary to other factors. Taken from Ballantyne et al. [4].

patients does not match descriptors in those addicted through illicit drug use, yet it shares many characteristics. Clinically, the important issue is that this state, whether it reaches “addictive” levels or not, requires treatment that is similar to validated and established opioid addiction treatment, namely drug maintenance therapy versus abstinence, together with, importantly, counseling. And these are pain patients, so they need additional help with managing their pain, preferably by nonpharmacological means.

What defines failed opioid treatment, in my view, is treatment that requires escalating doses without benefit of improved analgesia, and with serious adverse consequences, including cognitive impairment, neuroendocrine and immune changes, poor sleep, and possibly addiction. The neuroadaptations described in this chapter explain why such a state is reached—more and more drug is needed, withdrawal is difficult, it is easy to be convinced that more drug is needed when less drug

might have better efficacy, and adverse effects are difficult to acknowledge because the sufferer is under the influence of drugs that impair cognitive capacity.

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Update on Opioid Switching and Methadone Safety

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Educational Objectives

At the conclusion of this presentation the participant will be able to:

1. Describe the basic pharmacology of opioids and their role in therapy in managing chronic cancer and noncancer pain.
2. Describe principles and practices that support safe and effective switching from one opioid to another, and between routes of administration and opioid dosage formulations.
3. Explain techniques used to render opioid dosage formulation “abuse deterrent” and provide examples of each technology currently on the market.

Introduction

Opioids are a mainstay of therapy in the management of moderate to severe pain. Fortunately, most opioids are available in a variety of dosage formulations and can be administered by multiple routes of administration including parenteral (subcutaneous, intramuscular, intravenous), neuraxial (epidural, intrathecal), oral (short- and long-acting tablets or capsules, oral solution), rectal, transdermal, transmucosal (sublingual, buccal) and topical. It is not an uncommon clinical situation to require switching a patient from one opioid to another opioid, from one dosage formulation to

another, or even from one route of administration to an alternate route. Some reasons that lead to opioid switching include lack of therapeutic response, development of adverse effects, difficulties with medication administration (e.g., a change in patient status), and other considerations (e.g., opioid availability, formulary considerations, and patient or family health care beliefs about particular opioids) [9]. For these reasons, it is imperative that pain and palliative care providers understand the principles that support the art and science of opioid switching, a practice commonly referred to as an opioid conversion calculation.

Approach to Opioid Switching

One best practice technique is to use a consistent process when embarking on an opioid switch. Gammaitoni et al. recommended a five-step approach to opioid conversion calculations, which allows for calculation of an effective *and* safe dose of the new opioid regimen [6]. The advocated steps are as follows:

Step 1: Globally assess the patient (e.g., symptom assessment) to assure an opioid conversion is the best course of action (e.g., instead of modifying the analgesic regimen in some other manner).

Step 2: Determine the patient’s total daily dose of the current opioid. This total includes scheduled doses of opioid, plus an average of “as needed” doses.

Step 3: Decide which opioid analgesic and route of administration will be used for the new regimen, and calculate the new dose using an equianalgesic conversion chart (see Table I), recognizing the limitations of the data.

Step 4: Individualize the dosage based on assessment information gathered in Step 1 and ensure adequate access to medication for breakthrough pain.

Step 5: Monitor the patient's response to the new regimen, including therapeutic effectiveness (e.g., meeting the pain goal) and potential toxicity. Modify the analgesic regimen as appropriate (increase or decrease dose or alter the dosing interval) [6].

In switching from one opioid regimen to another, practitioners usually consult a chart that contains the best evidence of equipotent ratios between opioids (an example is shown in Table I) [7]. Hypothetically, using these estimations of equivalent potency should provide an equianalgesic dose, which is defined as "that dose at which two opioids (at steady state) provide approximately the same pain relief" [11]. Despite such a chart representing the best possible evidence available, it is not a guarantee of dose equivalency when switching from one opioid to another (or from one route of administration to another). Some of the data used to assemble this reference chart come from single-dose cross-over studies, and others are from steady-state cross-over trials. Patient-specific considerations such as age, sex, pharmacogenomic status, organ function, and level and stability of pain control generally are not standardized when evaluating equivalent potencies. Given these limitations, a healthy dose of clinical acumen and common sense is necessary when performing these calculations. Consider the following case as an example.

JS is a 72-year-old man with general debility, significant renal impairment, and low back pain. The patient has been receiving long-acting oral morphine 30 mg by mouth every 12 hours for the past several months with good success, but he has developed visual and auditory hallucinations over the past few weeks. Other causes have been ruled out, and the prescriber is concerned that these effects may be due to accumulation of morphine metabolites. The prescriber asks that you calculate an equivalent regimen of oral oxymorphone.

You have assessed JS's pain and agree that an opioid therapy is appropriate and that a switch to oxymorphone may be worth a try. He is not taking any morphine for breakthrough pain, so his total daily dose

(TDD) is 60 mg oral morphine. Set up an equivalency ratio as follows:

$$\frac{\text{"X" mg TDD oral oxymorphone}}{60 \text{ mg TDD oral morphine}} = \frac{10 \text{ mg oral oxymorphone}}{30 \text{ mg oral morphine}}$$

After cross-multiplying and solving for "X" you calculate a total daily dose of 20 mg oral oxymorphone as an equivalent regimen. Because we are switching from one molecular entity to a different molecular entity (e.g., from morphine to oxymorphone), it would be prudent to reduce the calculated dose by 25–50%. A 25% reduction would calculate to oxymorphone 15 mg per day, which we can administer as the oral long-acting oxymorphone 7.5 mg by mouth every 12 hours.

The last (and most important step) is to carefully monitor the patient's response over the next 7–14 days to assure that the therapeutic goal is being met, while avoiding toxicity. The prescriber may choose to add a short-acting opioid "as needed" for additional pain.

Safety Considerations with Opioid Switching

Shaheen et al. and Fine and Portenoy provide additional guidance when using an equianalgesic table such as one shown in Table I [5,11]. Specific recommendations include the following:

- Calculate the equianalgesic dose of the new opioid based on the equianalgesic table.
- When switching to a different opioid (excluding methadone and fentanyl), automatically reduce the calculated dose to be 25–50% lower than the calculated equianalgesic dose. Use clinical judgment regarding the magnitude of the dosage reduction. If the rotation is secondary to uncontrolled pain, use the equianalgesic dose (in other words, do not reduce the calculated dose).
- If considering switching opioids because of an adverse effect, consider instead reducing the opioid dose and using adjuvant analgesics to provide an opioid-sparing effect.
- While many practitioners commonly use the "2 mg/day oral morphine ~ 1 µg/hour transdermal fentanyl" rule when switching to transdermal fentanyl, Fine and Portenoy recommend using the equianalgesic dose ratios included in the package

insert, which are far more conservative (e.g., 60–134 mg/day oral morphine ~ transdermal fentanyl 25 µg/hour) [1,4,5].

- Fine and Portenoy recommend a second evaluation for dosage adjustment based on consideration of the severity of the pain at the time of the switch

and the presence of other medical or psychosocial factors that could alter the intended therapeutic outcome. For example, as described above, in a patient with severe pain, the second evaluation may result in the conclusion to negate the automatic dosage reduction considered in Step 1 (in

Table I
Equianalgesic opioid dosing

Drug	Equianalgesic Dose (mg)		Formulation Comments
	Parenteral	Oral	
Morphine	10	30	Available as short-acting tablets and capsules, and oral solution (including oral concentrate Roxanol). Available as oral long-tablet tablets and capsules (MS Contin, Oramorph SR, Kadian, Avinza). Available as rectal suppositories (equivalent dosing to oral).
Buprenorphine	0.3	0.4 (sublingual)	Available as sublingual tablets and injection. Available as 5, 10, 15, 20 µg/h 7-day patches in United States. Transdermal 4-day patches available (not in the United States).
Codeine	100	200	Codeine is a prodrug, metabolized to morphine by the liver. Most commonly administered in combination with acetaminophen (e.g., Tylenol #3). The U.S. FDA has removed from the market single-ingredient codeine sulfate oral tablets and codeine phosphate injections and combination products containing codeine phosphate.
Fentanyl	0.1	NA	Available as injection, transmucosal, and transdermal. Refer to reference source for further discussion of transmucosal and transdermal dosing of fentanyl, respectively.
Hydrocodone	NA	30	Oral solution (Hycodan) contains hydrocodone and homatropine. Most commonly given in combination with acetaminophen (Lorcet, Lortab, Vicodin, others).
Hydromorphone	1.5	7.5	Available as oral tablets, solution, injection, and rectal suppository.
Meperidine	100	300	Available as tablets, syrup, oral solution and injection. Not recommended for routine clinical use.
Methadone			Available as oral tablets and oral solution (including oral concentrate). Dispersible tablet not used for chronic pain management (only for opioid treatment programs). Refer to reference source for guidance on methadone conversion calculations.
Oxycodone	10	20	Available as short-acting oral tablets, capsules, oral solution (including oral concentrate OxyFast, Roxicodone). Available as a long-acting oral tablet (OxyContin). Frequently given in combination with acetaminophen (e.g., Percocet). Parenteral formulation is not available in the United States.
Oxymorphone	1	10	Available as a short-acting tablet, oral long-acting tablet, and parenteral formulation.
Tramadol	100	120	Available as a short-acting tablet, extended-release oral tablet, and injectable. Parenteral formulation is not available in the United States.

Source: Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing, Table 1-1 Equianalgesic Opioid Dosing, Copyright 2014 ASHP. Used with permission.

Note: Equianalgesic information presented in this table is that which is most commonly used by health care practitioners, but it is approximate. The clinician is urged to read caveats published with the original work, along with the text, and use good clinical judgment at all times [7].

other words, no dose reduction from the calculated dose). However, for a patient with moderate pain, the presence of confusion, multiple interacting medications and so forth, it may be prudent to reduce the calculated dose an additional 15%. [5] Of course, it would be important to provide adequate analgesic for breakthrough pain in case the calculated dose is too conservative.

Webster and Fine recommend a more draconian method for opioid switching [12]. They recommend starting the new opioid regimen at a dose used for opioid-naive patients (or the lowest available dosage formulation strength) while reducing the current opioid by 10–30%. The original opioid regimen would be reduced by 10–25% per week while increasing the new opioid by 10–20% each week based on clinical efficacy and safety. This method could take up to 1 month to complete. The authors recommend providing sufficient immediate-release opioid to manage increased pain or withdrawal symptoms. This method requires great patience on the part of the patient and practitioner, but it may provide a greater margin of safety in the long run.

Safe and Effective Methadone Therapy

Methadone is an intriguing opioid, with fairly complicated pharmacodynamic and pharmacokinetic properties, that is best dosed by experienced practitioners. The use of methadone is growing because of its significant cost-effectiveness and therapeutic efficacy. However, it is critically important that practitioners evaluate whether a patient is an appropriate candidate for methadone therapy (e.g., cardiovascular risk status, ability to adhere to the prescribed regimen, having a reliable caregiver), and pay careful attention to dosing in both opioid-naive and opioid-tolerant patients.

Updated clinical guidelines were published recently to increase safe prescribing of methadone for treatment of both opioid addiction and chronic pain [3]. A complete review of these guidelines is beyond the scope of this chapter; the guidelines address patient assessment and selection, patient education and counseling, baseline and follow-up electrocardiograms, monitoring for and management of adverse events, urine drug testing, drug interactions, and methadone use in pregnancy. Important to this chapter is the discussion

on the initiation of methadone in both opioid-naive and opioid-tolerant patients.

For patients with no prior exposure to opioids, the guidelines recommend a methadone starting dose in appropriate patients not to exceed 2.5 mg every 8 hours, with initial dose increases of no more than 5 mg/day every 5–7 days. Larger weekly increases (e.g., 10 mg/day) may be considered once the patient reaches a total daily dose of 30 or 40 mg/day, and then only when the benefit clearly outweighs the risks of therapy [3].

When converting to methadone from other opioids, there are many published recommendations that range from a 1:3 (oral methadone : oral morphine) to 1:20 conversion strategy [8]. This strategy is consistent with more general guidelines to reduced calculated equianalgesic doses by up to 90% when switching to methadone [3,5]. Interestingly, Salpeter and colleagues reported switching opioid-tolerant patients to methadone at a total daily dose between 2.5 and 15 mg, with excellent results. [10]

The American Pain Society guidelines recommend when switching from “higher” doses of other opioids to methadone to start at no higher than 30–40 mg/day, with initial dose increases of no more than 10 mg/day every 5–7 days. This strategy was effective in a case series published by Chatham et al. [2]. The authors reported a series of 10 patients receiving high-dose oral morphine or morphine equivalent (defined as >1200 mg/day). A fixed maximum methadone dose of 30 mg/day (10 mg by mouth every 8 hours) produced clinically meaningful improvements in pain scores without adverse drug effects in the majority of patients.

Conclusion

The ability to safely and accurately switch patients from one opioid regimen to another is a critically important skill for pain management and palliative care practitioners. There are several limitations to the equipotency data we currently have available, but they do provide some guidance, especially when combined with clinical judgment and common sense. Recent publications have provided additional suggestions to enhance safety when doing these calculations. Importantly, recent literature continues to support the potency of methadone when used as an analgesic, and in most cases, less is more. Practitioners are urged to use a conservative approach to opioid conversion calculations, with close attention

to detail and an adequate plan for unrelieved breakthrough pain.

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Opioid Prescribing for Chronic Pain, Prescription Drug Abuse, and Emerging Practice Standards and Regulation in the United States

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Educational Objectives

1. Review the U.S. problem of prescription drug abuse and opioid prescribing for chronic pain.
2. Review the evolving practice standards in the United States related to opioid prescribing for chronic pain.
3. Review changes in U.S. public policy and regulation on opioid prescribing for chronic pain in response to prescription drug abuse.

Introduction

With their many benefits and risks, opioids have long been associated with the management of pain. More recently, they have too often been conflated as one and the same. Over the past two decades, rising overreliance on opioids in the management of chronic pain in the United States has been associated with consumption rates that are disproportionate to those of other countries and an epidemic of prescription drug abuse. As significant risks in the treatment of chronic pain with opioids have been increasingly and convincingly demonstrated, including a high rate of unintended overdose deaths, U.S. public policies and professional practice standards are responding in step [1]. This response represents a major social and medical transition in response to the growing body of evidence describing risks tied to chronic opioid therapy, particularly at high

doses, relative to the inadequate or weak evidence base for their benefits, particularly benefits that are sustained over time.

The exact cause of the nation's overreliance on opioids for chronic pain in the United States and the epidemic of prescription drug abuse is not certain, but several factors seem to be interrelated. In the years prior to the recognition of this public health crisis, major regulators of U.S. hospital systems began to require assessment of pain with all clinical encounters [12]. Heightened recognition of pain management as an expected part of health care has been a compassionate and rational evolution in U.S. medicine; however, it may have escalated faster than the necessary education to support the knowledge base on safe and effective treatment of pain. In part, the experience of improving quality of life through liberalizing opioid use for patients with terminal illness may have been inaccurately extrapolated to populations with chronic illness and pain. Furthermore, the safety associated with the use of opioids was informed by data that are now understood to be weak and unable to support such conclusions [13].

Although pain has become much more widely assessed, knowledge of appropriate diagnosis and treatment continues to be limited at all levels of education for health care providers across all clinical professions [5,9,10,15]. Moreover, resources for complex patients in pain continue to be limited, with lop-sided access to

pharmacological and injection-based treatments compared with evidence-based approaches that address psychosocial or physical rehabilitation. Patient satisfaction surveys are increasingly employed by U.S. hospital or health systems to score and benchmark clinicians. However, exactly how much the results drive prescribing or quality is not known [2,4]. Time with complex patients is a diminishing commodity in U.S. health care, a problem that stands in contrast to the heightened needs of complex patients in pain who often require substantial time for assessment and treatment planning, as well as other forms of care and support.

In 2014, two counties in the state of California as well as the city of Chicago filed civil lawsuits against several drug-manufacturing companies. These lawsuits charged pharmaceutical companies with illegal marketing practices that have led to the problem of excessive use and abuse of prescription opioid drugs. The mayor of Chicago was quoted as stating: “For years, big pharma has deceived the public about the true risks and benefits of highly potent and highly addictive painkillers in order to expand their customer base and increase their bottom line” [8]. As the cases against these pharmaceutical companies have only recently been filed, the role of industry in the U.S. prescription opioid problem may be clarified more fully in the near future. Nonetheless, the conflict of interest between industry and health care is an area of considerable attention. Little has been published about the conflict of interest inherent in how prescribers are reimbursed. In the United States, reimbursement of clinical services typically incentivizes efficiency, which devalues time. It stands to reason that in the face of inadequate education and knowledge, dwindling resources, and limited time, busy clinicians view providing a prescription as one of their few efficient options.

Consumption of prescription opioids in the United States is excessive despite their higher risks relative to the many other options for safe and effective treatment of chronic pain [1]. A 2011 U.S. Institute of Medicine (IOM) report estimated that 100 million Americans are in chronic pain [9]. This finding stands in contrast to widely reported figures indicating that the nation consumes 80% of the world’s supply of opioids and 99% of the world’s supply of hydrocodone [11,16,17]. Recent federal, state, and professional policy changes are addressing the public health issues associated with escalating opioid use and overdose deaths. These new policies establish high expectations for safe use, adequate monitoring,

and early and ongoing risk management. They stress heightened and transparent risk management, and they recognize that chronic opioid therapy, and particularly high-dose opioid therapy, should not serve as the mainstay of treatment for chronic pain because most patients in chronic pain need much more than a single remedy or drug.

Regulatory and Policy Revisions

The U.S. Food and Drug Administration (FDA) announced new labeling for extended-release and long-acting opioids in September 2013 [6]. The new guidance to prescribers highlight the serious risks associated with opioids including misuse, abuse, neonatal opioid withdrawal syndrome, addiction, overdose, and death. It calls for greater caution in opioid prescribing, increased monitoring and additional patient education. The FDA states that extended-release, long-acting opioids are “indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate” [6]. Treatment decisions are to be based on carefully weighing the substantial risks of chronic opioid therapy against the potential benefits in relation to an individual’s particular condition. In addition, the new regulation also requires drug manufacturers to pay for post-marketing outcomes studies.

The Federation of State Medical Boards of the United States (FSMB) revised its Model Policy for the Use of Opioid Analgesics in the Treatment of Chronic Pain in August 2013 [3]. This policy advises U.S. medical boards on best clinical practices for opioid prescribing for chronic pain (Table I). It stresses the potential risks of opioid therapy as well as the expectation of a complete evaluation and risk assessment before and after chronic prescribing of an opioid. It emphasizes the essential role of acquiring informed consent. The model policy provides details around expectations that prescribers clearly explain to patients the potential risks of opioids, including the risks of dependence, addiction, and overdose, the risk of impaired motor skills (affecting driving and other tasks), and other risks. Obtaining informed consent and completing a shared treatment agreement is presented as an opportunity for providers and patients to engage in fully understanding the goals of treatment, the specific policies and expectations associated with the

treatment, the responsibilities of the prescriber and the patient for safe medication use, the patient's consent for periodic adherence monitoring such as drug testing or use of a prescription drug monitoring program, and the physician's responsibility to be available to care for unforeseen problems. Compared with the most recent prior revision in 2004, this policy offers much more comprehensive and detailed guidance. It advises U.S. state medical boards that prescribers of opioid therapy for chronic pain should be expected to engage in significant assessment of whether opioids are clinically indicated at the time of prescribing and to continue significant assessments throughout prescribing. It stresses early and ongoing assessment of risks associated with opioids. Such assessment should occur prior to escalating opioid dose or excessive reliance on high-dose opioids and includes use of available tools for risk mitigation, monitoring of objective outcomes, patient education, and attention to risks or alternative treatments (Table I).

The U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) recently released opioid overdose prevention toolkits for prescribers, first responders, patients, family members, and the general community [14]. These toolkits offer common-sense approaches for risk reduction such as making naloxone readily available and instructing first responders and community or family members how to use it early in overdose. Acquiring or using naloxone in this setting is a relatively new option in the United States, and the toolkits review who may benefit from this treatment option and how naloxone kits may be acquired. The toolkits also stress that patients should be made aware that it is illegal to sell, give away, or otherwise share their medication with others, including family members, and that it is their duty to keep the medication secure (use a locked cabinet, restrict access, safely dispose of any unused supply, etc.). The

U.S. FDA recently approved a pharmaceutically manufactured naloxone auto-injector designed to deliver a dose of naloxone outside of a health care setting [7].

Although hydrocodone is the second most abused prescription opioid according to the U.S. Drug Enforcement Agency (DEA), hydrocodone products are the most prescribed drugs in the United States. The high rate of hydrocodone prescribing in this country may be related to its less restrictive classification as a controlled substance; most of the abusable opioids other than hydrocodone are grouped as Schedule II controlled substances, rather than the less restrictive Schedule III (hydrocodone is Schedule III). In October 2013, the U.S. FDA announced its support for rescheduling hydrocodone-acetaminophen products from Schedule III to Schedule II. This decision reflects widely held concern that the current scheduling inaccurately implies that hydrocodone has less risk of abuse than other opioids. Since hydrocodone is the most prescribed drug in the United States, moving it into a more restrictive prescribing class may unfortunately pose adversity for some patients, pharmacies, and prescribers. On balance, however, this action seems justified by our current alarming prescribing rates and abuse patterns as well as the growing knowledge base informing clinicians about the risks associated with prescribing opioids for chronic pain.

Conclusions

The policies reviewed here offer coherent and consistent guidance for U.S. prescribers and regulators. However, they also raise awareness of the insufficient body of research on analgesic alternatives to opioids, the minimal education received by U.S. providers on pain and pain management across the spectrum of learning from prelicensure training through continuing professional education, as well as the impact of inadequate reimbursement

Table I
Summary of elements of departure from accepted best clinical practice

Inadequate assessment of whether opioids are clinically indicated
Inadequate determination of risks associated with opioid use
Inadequate monitoring of outcomes during the use of potentially abusable medications
Inadequate education of patients
Failure to obtain substantive informed consent
Inadequate attention to risks or alternative treatments when escalating opioid doses
Excessive reliance on opioids, particularly high dose opioids, for chronic pain management
Inadequate use of available tools for risk mitigation (i.e., prescription monitoring programs, drug testing, etc.)

Source: The Federation of State Medical Boards of the United States (FSMB) revised Model Policy for the Use of Opioid Analgesics in the Treatment of Chronic Pain [3].

for the types of pain treatments that are known to work, but take more time or resources to provide than a prescription for a pill. Hopefully, the U.S. experience may offer the international community a useful perspective and help to advance safer, more effective, and sustainable treatments for chronic pain management.

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Chronic Opioid Clinical Management Guidelines for Wisconsin Worker's Compensation Patient Care

Emerging medical evidence shows that the previously pursued practice patterns of using higher dose chronic opioids rarely results in sustained improvements in pain control and function, but has resulted in increased addiction and death nationally over the last 10 years. These Clinical Guidelines will assist you in managing your patients with chronic pain.

For any worker's compensation patient who will need opioid treatment for a period of more than 90 days, the treating physician should follow these guidelines and or consider referral to a Pain Management specialist.

The following steps for patients who require chronic opioid treatment for a worker's compensation injury should be followed:

1. The Pain Generator Must be Adequately Evaluated

- A clear etiology and diagnosis of the pain should be identified and documented at every visit. "Chronic Back/Neck Pain" is a symptom, not a diagnosis.
- Not all pain conditions are opioid responsive; therefore, not all diagnoses that cause pain are appropriate for chronic opioids. Chronic headaches and fibromyalgia would be examples of diagnoses that are not appropriate to be treated with chronic opioids.
- If you are not able to identify (a) specific medical diagnosis(es) responsible for the patient's pain, then consider that the patient has not been properly worked up for a pain generator or the patient does not have a medical diagnosis that warrants the use of chronic opioid therapy. If the patient requires further work up, document what the evaluation plan is while the patient is on the opioids (initial visit and possibly thereafter if indicated).

2. Non-opioid Options Need to be Presented to the Patient

- Opioid therapy truly needs to be considered a last resort.
- All alternative treatment options must be discussed with the patient.
- Some examples of non-opioid therapy would be chiropractic treatment, physical therapy, cognitive behavioral therapy, massage therapy, local injections, non-opioid pain medications, surgery, integrative medicine and TENS units.

3. Patient Criteria for Long Term Opioid Therapy?

- The following criteria help to identify appropriate candidates (all of these should be specifically documented in the medical record):
 - Patients **must** have persistent (i.e. daily) moderate to severe pain (pain 5 and over on the 10 point scale).
 - Patients **must** have daily, describable functional limitations due to pain.
 - Identifiable medical diagnosis, known to be appropriate for chronic opioids therapy (i.e. the pain generator/Diagnosis is not chronic pain syndrome, pain, or headache etc).
 - **Minimum risk profile as identified by standard screening (SOAPP recommended).** Formalized risk assessment on the first visit should be done using an established tool, such as SOAPP (a self-report questionnaire available online that the patient fills out and you score. SOAPP information can be found at www.painedu.org/soapp-development.asp and downloadable at the same site after registering).
 - Absence of or, if present, concurrent treatment with psychiatrist of coexistent psychiatric conditions should be included.
 - Patient is not actively using illegal substances (**urine drug screening before starting chronic opioid therapy is imperative**). Part of the risk assessment should include searching the Prescription Drug Monitoring Database (the State-housed depository of all

controlled Substance prescriptions filled at any Wisconsin pharmacy for every person that receives a scheduled medication, accessible for registration at <http://dsps.wi.gov/Default.aspx?Page=cccf5c16-98f8-41c6-8906-ce29763de6c4>) prior to writing a prescription for any scheduled medication. This enables you to identify whether or not the patient is getting opioids or other scheduled medications from a provider other than you and therefore exhibiting a high risk behavior or potentially violating the treatment agreement.

- **Lack of other aberrant behaviors (make certain to carefully review the patient's past history for evidence of failure to follow previous opioid treatment agreements).** Consider searching the Prescription Drug Monitoring Program (pdmp@wisconsin.gov) and or the Wisconsin Circuit Court site, at <http://wcca.wicourts.gov/index.xsl> to help identify if the patient has had any previous drug-related legal problems, which can identify at-risk individuals.
- Potential chronic opioid therapy benefits should outweigh the risks.

For patients with high SOAPP scores and unclear clinical conditions, consideration can be given to not offering chronic opioid therapy because the risks outweigh benefits. If the patient is already on them, they could be appropriately discontinued.

If the patient is not appropriate to receive chronic opioids for the pain condition, clearly explain in your note, and why you came to that conclusion.

4. Required Documentation and Management on Initial and Subsequent Visits for Patients on, or Starting, Chronic Opioids

- Informed consent discussion documented on the first visit.
- Opioid treatment agreement ("narcotic contract") should be signed before starting opioids and yearly afterwards.
- **Chronic opioid therapy is a goal-directed therapy, and goals must be stated so that if they are not met, the medications can be appropriately discontinued.** Goals of chronic opioid therapy include
 - **Sustained** pain reduction (at least 30% as compared to pre-treatment).
 - **Sustained** functional improvement.
 - Strict compliance with the opioid treatment agreement.
- It is important to have objective information regarding pain and functional abilities that can be followed over time in order to ensure that therapy goals are being obtained and sustained; therefore, **such assessment needs to be documented at each visit.**
 - Pain assessment using the standard 10-point pain scale is appropriate. In addition, it is often helpful for the patient to rate "best pain," "average pain" and "worst pain" on the 10-point scale.
 - The Oswestry scale can be used for low back pain patients. The Brief Pain Inventory (long or short forms) and/or SF-12 can be used for all types of pain patients. All are self-report scales and available online.
- The Oswestry Disability index with instructions can be found and downloaded from http://www.aadep.org/documents/filelibrary/presentations/pmd_evaluation_martin_and_pilley_aafp/Appendix_D_The_Oswestry_Disability_E42C3CC567278.pdf
- The Brief Pain Inventory can be downloaded from <http://www.partnersagainstpain.com/printouts/A7012AS8.pdf>
- The SF-12 can be downloaded from <http://ckm.osu.edu/sitetool/sites/orthopublic/documents/research/trauma/SF12.pdf>
- Document the patient's general appearance, functionality in the office setting and mentation to show that there are no observable adverse effects or toxicities associated with medications. Also,

document whether or not these observations are consistent with whatever pain ratings the patient provides. This should be done every visit.

- **The SOAPP tool should be re-administered any time the patient shows any aberrant behavior**
- Visit intervals of no longer than once every month while you are actively titrating any patient are advisable. The patient is in the titration phase any time you are actively adjusting medications and it is not appropriate to adjust medications and have the patient return at intervals greater than 4 weeks. Stable patients can be seen every other month.
- Consider explaining to patients on higher doses of opioids that newer clinical evidence demonstrates that lower doses of opioids are just as effective in maintaining sustained functional improvements and pain reductions and are safer; therefore, you would like to begin to wean the medications and closely follow the patient's functional and pain scores. Very frequently, as opioids are weaned, patients have minor and short-term/self-limiting increases in pain scores with no significant functional decline and they do just fine as the opioids continue to be weaned.
- Address known side effects. It is highly unusual for a patient who is compliant with taking chronic opioids to ***not*** have constipation; therefore, all patients should be on appropriate medication (Senna or Miralax are good choices). If a patient claims to not be constipated, consideration should be given to diversion/noncompliance and immediate urine drug screening is recommended. Of course, it is always possible a compliant patient is not constipated, but that is the exception, not the rule.
- **Compliance monitoring is mandatory for all patients on chronic opioid therapy, regardless of age.**
 - Urine drug screen first visit and with aberrant behavior.
 - Pill counts thereafter and/or unannounced urine drug screens.
 - Make certain to be familiar with the limitations, if any, of the specific urine drug screen that you are performing. For example, some "standard" drug screens do not identify synthetic opioids even if the patient is taking them as prescribed.
- **Clinical Management Tool: Always assess and document **The Five A's**:**
 1. **Analgesia** – adequate pain relief with opioids,
 2. **Activity increase** – increase in activities and function,
 3. **Adverse effects** – such as drowsiness and mental changes that effect function suggest inappropriate use,
 4. **Aberrant behavior** – such as stolen or loss of opioids, frequent refills, obtaining opioids from multiple physicians or Urine Drug Test revealing NO opioids or other non-prescribed drugs, and
 5. **Affect** – changes in mood-more depression and anxiety with opioids (Remember that when opioids are used appropriately the individuals function and mood improves and when used inappropriately the individuals function and mood or adversely effected)

5. Opioid Dosing and Guidelines

- **Chronic opioid therapy is a goal directed therapy. If the patient is not meeting the goals of therapy, opioids should be discontinued.**
- The following lists general morphine dose equivalents (MDE), which can facilitate conversion from one opioid to another (all in oral doses). Specific cross-tolerance varies from patient to patient and so care need be taken when converting from one to another.
 - 30 mg of morphine = 20 mg of oxycodone = 6 mg of hydromorphone = 10 mg of oxymorphone = 20 mg of hydrocodone = 120 mg of codeine
 - 50 mg of morphine = 25 mcg of transdermal fentanyl (this varies widely from 30 to 134 mg or morphine)
 - Buprenorphine patches 5 mcg = 10 mg morphine

- Methadone is a high risk drug and consideration should be given to not using it unless you have advanced training in pain management or the use of methadone.
- “Atypical” pain medications such as tramadol (immediate and extended release forms) and tapentadol (immediate release) can often be used instead of opioids and tend to have less problems with diversion and abuse.
- Oxycodone is highly desirable on the street and there are many other opioid alternatives; oxycodone products should be considered the last line opioid.
- It is becoming increasingly popular to treat patients with very high doses of immediate release opioid without the use of an extended release opioid. There is absolutely no physiological/pharmacological reason that immediate release products work fine but extended release products “don’t work for me.” Generally, this is because the immediate release opioids are much easier to abuse and divert than the extended release opioids, not because the extended release opioids “don’t work.”
- Once a patient reaches an opioid dose of 50 mg MDE, then the patient should be placed on an extended release opioid product.
- Not all pain is opioid responsive and, by the time you get to 120 MDE, if the pain is opioid responsive, the patient should report some sustained improvements in pain and function.
- Recent information indicates that doses over 120 mg MDE usually do not provide increased analgesia compared to doses under 120 MDE. This is considered a dosing “soft ceiling” and so if this dose is breached, be certain to clearly document what goals are expected to be attained with dose escalation. If the patient doesn’t meet goals by a dose of 180 – 200 MDE, then the patient has opioid-unresponsive pain and the opioids should be appropriately discontinued.
- There is no clinical evidence that doses above 200 MDE per day result in improved analgesia. Doses of 200 MDE per day or above have 9 times the chance of adverse events. This is considered a dosing “hard ceiling” such that rarely this dose needs to be breached.

6. Alternative Pain Medications to Opioids

- Because there are many other chemical systems that participate in maintaining pain, it is perfectly reasonable to start **other adjunctive medications (tricyclics, SSRI’s, gabapentin, tizanidine, other anticonvulsants, duloxetine, etc.) to help with chronic pain management at any point in the patient’s treatment.** Such adjunct medications should be used in conjunction with taking advantage of side effects they may have that are beneficial (sleep induction for tricyclics and trazadone, for example).
- Daily dosing of “muscle relaxers” is **not indicated** for the treatment of chronic pain but may be helpful in treating their disordered sleep. **Carisoprodol specifically is NOT recommended for this purpose (oxycodone + diazepam + carisoprodol = “the holy trinity” on the street).**
 - Cyclobenzaprine immediate release or extended release is often effective and well tolerated at bedtime.
- **If benzodiazepines have been prescribed specifically as part of the patient’s pain reduction treatment, then consideration should be given to discontinuing via a taper.** There is no evidence that this class of medication helps with pain reduction and adverse medication effects are many times more likely when patients are on benzodiazepines and opioids together. If benzodiazepines and opioids are necessary, then consultation with psychiatry is recommended to assist with whatever condition for which the benzodiazepines are needed since they are not indicated for management of chronic pain.

7. Addiction, Pseudoaddiction and Aberrant Behaviors Definitions

- Physicians improperly using the terms “addiction” and “drug seeking” is common in chronic pain management; however, “drug seeking” and “addiction” are not necessarily the same thing and they both have very negative stigma for our patients. **Please use the appropriate terminology** in your documentation.
- Likewise, “tolerance,” “physiologic dependence” and “addiction” are **not** the same thing. Do not use them interchangeably. Tolerance is the ability to “get used to” the medication such that increasing doses are needed over time in order to achieve the same results that had been achieved at lower doses of the substance. Physiologic dependence is a normal and totally expected outcome of using certain classes of substances (beta blockers, digitalis, benzodiazepines, opioids and alcohol) and is evidenced by identifiable withdrawal syndromes. The entities are different and documentation should not reflect confusion of the concepts.
- Addiction means that a patient is displaying particular maladaptive psychological behaviors associated with the opioid. If you think the patient is truly “addicted”, you must refer the patient to a licensed practitioner for appropriate treatment. Indicators of addiction include:
 - Any indication that the patient is using the pain medication for anything other than pain relief (frequently expressed as “I feel better” even though the objective pain assessments and functional scores are no better than pre-treatment or the patient vigorously objecting to changes in medication regimen when there is no objective evidence present opioid therapy is achieving any pretreatment goals).
 - Despite negative consequences directly related to the patient inappropriately taking/obtaining the medication (missing work, loss of personal relationships, stealing/lying to get more opioids, etc.), the patient cannot address them/stop taking the medication because the desire for the substance outweighs all else.
 - Craving the opioid for no apparent reason (i.e. pain doesn’t drive the desire for the drug).
 - **Inability to reduce their medication dose even though the plan is to wean off the medication.** This is a strong indicator of addiction. The non-addicted patients will typically wean off the medications as directed (provided that the titration is slow enough to avoid withdrawal). However, patients who are addicted will not be able to follow the directions.
- **“Aberrant behavior” is a general term describing abnormal patient behavior revolving around their opioid medications. Common examples of aberrant behavior include:**
 - Request for early refills, **for any reason**
 - Noncompliance with the treatment agreement
 - Known criminal activity surrounding their medications or illegal substances “accidental” or purposeful)
 - Evidence of intoxication of any substance
 - Incorrect pill counts
 - Drug screen abnormalities
 - Patients admitting they use their medications for any purpose other than pain control (“I get high”, “I like how they make me feel”)
- Sometimes, a patient with certain (not all) aberrant behaviors may be demonstrating them because pain is undertreated (e.g. criminal activity is never a reasonable sign of undertreated pain). This type of patient realizes that when more opioid than prescribed is taken, pain is reduced and function improved. This type of behavior is called **“pseudoaddiction.”** Pseudoaddicted patients are often branded “addicts” and “drug seekers” as they try to find pain relief and, often, they run out of medication early, and sometimes also seek opioids from other providers. For this patient, if he or she receives the proper dose of opioid, their aberrant behaviors cease. Therefore, it is important to properly identify **why** the patient is exhibiting aberrant behaviors.
- **Therefore, not all patients with aberrant behaviors are addicted.** The problem is that, many times, as soon as one or more aberrant behaviors are identified, the patient is labeled a “drug seeker” or “addicted.” That is not always true. It is important to understand this so that the true

nature of the aberrant behavior is identified and dealt with properly and so that the patient does not become inappropriately labeled, stigmatized and, especially, improperly treated.

- Clinical Management Tool: Assess and document **The Four C's** seen with addiction are:
 1. **C**ompulsive use,
 2. **C**ontinued use despite harm,
 3. **C**ravings for the drug, **and**
 4. **C**ontrol impaired, over the use of opioids

8. Tapering and Discontinuing Opioids

- It is perfectly valid (at any point in treatment), to determine that the patient is not an appropriate candidate for long term opioids. State the reasons why clearly in your note. Indicators that the patient is not appropriate for chronic opioid therapy are basically that he or she does not meet their treatment goals or they are addicted. Consider the following as reasons to start to taper and discontinue chronic opioid therapy:
 - Unacceptably high risk assessment (SOAPP) scores.
 - Evidence of addiction (must refer to addictionologist).
 - Noncompliance with opioid treatment agreement.
 - Failure to meet goals of therapy.
 - Opioid-induced hyperalgesia (fairly common), in which chronic opioid therapy patients become "hypersensitive" to pain, even to the point that non-painful stimuli elicit pain. Painful stimuli can cause uncontrollable pain. The only way to treat this is to discontinue opioids.
- **If the patient is not a chronic opioid candidate, the medication must be appropriately discontinued.** Because of the expected physiological dependence associated with this class of medications, the patient's opioid dose needs to be titrated down. Titration also allows for the assessment of whether or not the patient may truly be appropriate for the opioid. If the patient has true opioid responsive pain that only responds to the higher doses of the medication, then as you titrate the dose down, there will be sustained and dose-dependent increases in pain and decreases in function. It is common that as opioids are weaned to off, patients have periods of slightly worsened pain and/or decreased function, but the majority of patients "get over these bumps" such that weaning is overall tolerated. If during the weaning process, a patient does have persistently increased pain (with consistently elevated pain scores) and decreased function (with consistently worsened functional scores), then it is reasonable to increase the opioid medication back to the lowest dose at which the patient was doing well in the medication wean.
 - Generally, decreasing the dose by 10% every three to five days is usually well tolerated but rates even slower than this are not unreasonable. The key is that the wean is tolerated so that the patient can get off the medication.
 - Do not change a patient from one opioid to another to "make weaning easier". Changing a patient to methadone or any other opioid in order to more easily wean them off their opioids is considered addiction medicine and one needs a special license from the DEA in order to do this. Simply leave the patient on the present opioid, document the patient is not appropriate for chronic opioid therapy and is not addicted but because of physiologic dependence the medication needs to be decreased slowly to avoid withdrawal and gradually lower the dose and follow them very closely (no more than once every four weeks).
 - Referral to an Addictionologist or Psychiatrist with experience in withdrawing and eliminating use of opioids should be part of the "exit strategy" in Chronic Opioid Treatment.

9. When should Subspecialty Consultation be Considered?

- For any worker's compensation patient who will need opioid treatment for a period of more than 90 days, the treating physician should follow these guidelines and or consider referral to a Pain Management specialist.

- Pain specialists can consult to evaluate:
 - And comment upon the appropriateness of chronic opioid therapy in a given patient.
 - And administer local injections for pain control in the case of pain generators that are known to respond to such.
 - Patients with aberrant behaviors.
 - Patients above the previously-described dosing ceilings and you cannot wean down.
 - Patients on methadone for pain control (methadone is a high risk drug and should only be used by specialists or practitioners trained to use methadone for pain control).
 - Opioid induced hyperalgesia.
- Any chronic pain patient who has not gone to physical therapy should be seen not only for home exercises but also for energy conservation techniques.
- Patients that are known to have active psychiatric diagnoses (bipolar, depression, schizophrenia, etc.) and/or on benzodiazepines are probably best co-treated with psychiatry.
- Cognitive behavioral therapy has been shown to be of significant benefit to chronic pain patients and, if available, should be requested.
- If the patient has been diagnosed with opioid addiction, then you must refer the patient to a licensed practitioner for appropriate treatment.

Chronic Opioid Assessment and Documentation Checklist

- Documentation of work up for etiology of pain with a **clear medical diagnosis** stating the specific pain generator(s) the diagnosis must be appropriate for chronic opioids (redocument every visit).
- Clearly state if the patient is appropriate for non-opioid therapy, such as PT, cognitive behavioral therapy, injections, etc.
- Address known side effects (every visit).
- Formalized risk assessment using SOAPP, COMM or DIRE on the first visit and intermittently if patient demonstrates aberrant behavior.
- **Document functional assessment at each visit** – as example with Oswestry scale or SF-12.
- Rate pain using 0 – 10 scale with rating of best pain, worst pain and average pain (every visit with specific relation of scores from past visits to now).
- Opioid agreement signed (initial and yearly afterwards).
- **Compliance monitoring** – Urine drug screen first visit and pill counts thereafter or unannounced urine drug screens.
- Informed consent discussion documented on first visit.
- Document general appearance and functionality every visit to show that there are no observable adverse effects associated with the medications.
- **Consider subspecialty referral or co-management in patients with aberrant behaviors, patients that score “high risk” on the risk assessment tool, opioid induced hyperalgesia and unclear pain conditions.**
- Is the Patient on more than 120 MDE? If so, clearly document why that is the case since there is very little evidence that doses higher than this benefit the patient.
- Is the Patient on more than 200 MDE? NO literature supports this as more effective than lower doses. Medication-related adverse events are 9 times more likely with these doses than at lower doses.
- Is the patient on a benzodiazepine and an opioid? If so, strongly consider discontinuing one or co-managing with psychiatry. There is no evidence that benzodiazepine use is of benefit in treating chronic pain and adverse events when mixed with opioids are very high.

Note that the referred-to standardized assessment tools are all available for download online (see reference section).

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HEALTH & HUMAN SERVICES

Massachusetts Passes Nation's 'Most Comprehensive' Law to Combat Drug Addiction

BY TRIBUNE NEWS SERVICE | MARCH 15, 2016

By Marie Szaniszlo

Beginning in July, Massachusetts hospitals will have to evaluate for substance abuse anyone who arrives at an emergency room suffering from an apparent opioid overdose.

The mandate is part of a bipartisan bill Gov. Charlie Baker signed into law yesterday in response to a drug crisis that claims nearly four lives each day in the state.

"May today's bill passage signal to you that the commonwealth is listening, and we will keep fighting for all of you," Baker said at a State House ceremony attended by families who have lost loved ones to addiction.

The law is "the most comprehensive measure in the country to combat opioid addiction," the governor said, and the first to limit an initial opioid prescription for adults -- and every opioid prescription for minors -- to a seven-day supply.

To prevent addicts from going from one doctor to the next in search of OxyContin, Vicodin and other opioid drugs, the law also requires doctors to check a prescription-monitoring program before prescribing them. And no one will be able to able to graduate from medical or dental school without passing a course in pain management.

"This problem used to be seen as a crime," state Senate President Stanley C. Rosenberg said. "It's now understood to be a disease" of self-medication "from pain and hopelessness."

Like many parents, Janis McGrory of Harwich never imagined that her child -- who graduated 10th in her high school class with plans to attend college, where she had a full scholarship -- would ever become a drug addict. But within two years of taking her first pill, she said, her daughter Liz found herself in a cycle of addiction, arrest, jail, detox and relapse, until she died five years ago of a heroin overdose at 23.

"I tried everything I could to help my daughter," McGrory said. "I stand here representing the thousands of grieving mothers who have lost children to this disease. ... It breaks my heart."

In 2014, there were 1,099 confirmed cases of unintentional opioid overdose deaths in Massachusetts, up 21 percent over the 911 overdose cases in 2013, according to the state Department of Public Health,

"To those who have lost loved ones, to those who have loved ones who are hurting, who are struggling, who are in pain, I recognize -- we all recognize -- that this legislation will not bring your loved ones back," Attorney General Maura Healey said. "But I want you to know and I hope that you find some measure and comfort knowing that today there is legislation that is going to change the course for other families."

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FDA will require warnings on immediate-release painkillers



Liz Szabo, USA TODAY

3:54 p.m. EDT March 22, 2016



(Photo: Sue Ogrocki, AP)

In an effort to stem the epidemic of prescription drug abuse, the [Food and Drug Administration](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491739.htm) will require its strongest warning (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491739.htm>) on immediate-release opioid painkillers.

The "black box" warning will alert users to the "serious risks of misuse, abuse, addiction, overdose and death" involved with taking opioids, a class of painkillers that includes morphine, [Vicodin](#) and Percocet. The warnings will appear on immediate-release painkillers, which are taken every four to six hours.

The FDA issued warnings on extended-released painkillers, which contain higher doses and are taken once or twice a day, in 2013. Extended-release opioids pose special risks, because people can crush them to produce a strong high, making them a target for abuse.

"The FDA remains steadfast in our commitment to do our part to help reverse the devastating impact of the misuse and abuse of prescription opioids," said FDA commissioner [Robert Califf](#) in a statement. "Today's actions are one of the largest undertakings for informing prescribers of risks across opioid products, and one of many steps the FDA intends to take this year as part of our comprehensive action plan to reverse this epidemic."

About 40 Americans die each day from overdosing on prescription painkillers, according to the [Centers for Disease Control and Prevention](#). In 2013, an estimated 1.9 million people abused or were dependent on prescription opiates.

The labels for immediate-release opioids will now say that they should only be prescribed when there are no alternative treatments. Drug labels will also note that taking opioids repeatedly while pregnant can cause neonatal opioid withdrawal syndrome, a potentially life-threatening condition in babies.

The FDA's announcement comes at a time of mounting concern over opioid addiction and overdoses.

Last week, the CDC released opioid prescribing guidelines for the first time. The guidelines urge doctors to avoid prescribing opioids for chronic pain unrelated to cancer or end-of-life care, noting that the drugs have serious risks but few demonstrated benefits.



USA TODAY

[Doctors told to avoid prescribing opiates for chronic pain](#)

[\(http://www.usatoday.com/story/news/2016/03/15/cdc-issues-new-guidelines-opiate-prescribing-reduce-abuse-overdoses/81809704/\)](http://www.usatoday.com/story/news/2016/03/15/cdc-issues-new-guidelines-opiate-prescribing-reduce-abuse-overdoses/81809704/)

Also last week, Massachusetts' governor signed the first law in the nation to limit a person's first opioid prescription to seven days. The law also provides education for students and doctors.

The FDA has been criticized for not doing enough to stem the opioid addiction crisis, particularly by Sen. [Edward Markey](#), D-Mass., who tried to hold up Califf's approval as a way to pressure the FDA to do more to fight addiction.

"Today's announced changes to the labels of opioid products will finally reflect what we have known about these drugs for decades — they are dangerous and addictive and can lead to dependency, overdose and death," Markey said in a statement. "It has taken FDA far too long to address the grave risks of these drugs that have claimed the lives of thousands this year alone."

Markey said the FDA needs to do more to protect patients. All new opioids should be reviewed by an advisory committee of outside experts, for example. Doctors also need more education about how to prescribe pain relief safely, he said.

The opioid epidemic: It's time to place blame where it belongs

RONALD HIRSCH, MD / PHYSICIAN | APRIL 6, 2016

The media is full of stories about the current opioid crisis. But unlike many national crises, such as the Flint lead-contaminated water crisis, the focus is on solutions and not blame. A few weeks ago, the Centers for Disease Control and Prevention issued [guidelines](#) for prescribing opioids in chronic pain, Congress approved funding for prevention and treatment, and the US HHS released a ["National Pain Strategy."](#)

So to fulfill my duty as an American, allow me to place blame for our current opioid crisis. Allow me to start with physicians. We overprescribe opioids, just as we overprescribe antibiotics. But it is generally well meaning; we don't want our patients to experience pain. Healthy Living magazine recently published a [heart-wrenching story](#) of a woman whose life was nearly destroyed by two weeks of oxycodone prescribed by a well-meaning physician for arthritis. These physicians can best be described as innocent bystanders. But "pill mill" doctors who set up shop, accept cash as the only payment and are willing to prescribe to anyone for any ailment, real or feigned, are criminals and need to be stopped. They cast a long shadow on the work of every other physician trying to help patients.

After the minor role of physicians come the real co-conspirators. First is Purdue Pharmaceuticals, the manufacturer of Oxycontin. Despite a [lack of increased efficacy](#) in treating pain compared to older medications, Purdue mounted an aggressive marketing campaign that included a [warning](#) from the FDA in 2003 over misleading advertisements. Physicians, including myself, believed Purdue and started using Oxycontin, thinking we were helping patients.

At around the same time as Oxycontin's approval, the [American Pain Society](#), introduced the "pain as the 5th vital sign" campaign, followed soon thereafter by the VA adopting that campaign as part of their [national pain management strategy](#). This declaration was not accompanied by the release of any device which could objectively measure pain, as was done with all previous vital signs, making it the first and only subjective vital sign.

The Joint Commission joins the list in 2001, issuing standards requiring the use of a pain scale and stressing the safety of opioids. According to the [Wall Street Journal](#), they even published a guide sponsored by Purdue Pharma. This guide reportedly stated, "Some clinicians have inaccurate and exaggerated concerns about addiction, tolerance and risk of death. This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control." The Joint Commission framed pain as a [patient's rights issue](#), inferring that inadequate control of pain would lead to sanctions.

Press Ganey deserves a place with their emphasis on patient satisfaction. They monetized their concept, selling not only surveys but also consulting services to help hospitals improve their scores. Unfortunately, the correlation between patient satisfaction and quality is unclear, with a [study from UC Davis](#) suggesting that high satisfaction is actually dangerous, correlating it to higher expenditures, higher rates of hospitalization and a higher risk of death. But acknowledging such literature would affect Press Ganey's lucrative survey sales, so such studies are ignored.

CMS determined that pay for volume CMS developed the value-based purchasing program to shift from pay for volume to pay for value. Hospitals are scored based on their performance on measures of processes of care, outcomes of care, efficiency and the patient experience. The patient experience is based on scoring on HCAHPS surveys that are sent to patients, which includes patient scoring of their satisfaction with their pain control. CMS decided that a patient's satisfaction was as important as whether a patient developed a hospital-acquired condition or even survived their hospitalization, and weighted satisfaction at 30 percent of the overall score.

Because CMS was now attaching significant reimbursement to patient satisfaction, hospital administrators developed initiatives to improve their scores and avoid a penalty. Because only 25 completed surveys a month are required, and the difference between the 50th percentile and 90th percentile can be an absolute difference of 1 to 2 percent, a single poor survey can have devastating effects. Administrators held physicians responsible for ensuring that every patient is completely satisfied in every way. As described in the comments section of a 2013 Forbes article entitled, "[Why Rating Your Doctor is Bad for Your Health](#)," administrators withheld pay or bonuses. Physicians felt pressured to prescribe opioids when patients demanded them, despite their reservations about the need for opioid medications. Thomas Lee, MD from Press Ganey in [JAMA](#) stated "these (drug-seeking) patients do not respond often to surveys and thus have little influence on physicians' overall ratings" but without any proof of such; depriving a potential drug-seeking patient who threatens to "give bad satisfaction scores" is a sure route to trouble.

CMS also tried to deflect blame in a [JAMA editorial](#), noting, "Because some hospitals have identified patient experience as a potential source of competitive advantage, these actions can create perverse and harmful incentives to elicit positive survey responses. For example, there are reports that some hospitals link individual physician or physician group financial incentives to performance on disaggregated HCAHPS responses. This is contrary to the survey's design and policy aim." If so, why did CMS not address this in 2013, when the Forbes article provided ample evidence that hospitals were using the surveys in such a way? A notice to hospitals forbidding the use of HCAHPS as a punitive measure would have gone a long way to empowering doctors to say "no" to patients demanding opioids.

Of course placing blame will not fix the current problem but neither will asking for the resignation of the governor of Michigan, but those responsible for this crisis need to be held accountable. I call on Congress to hold hearings and compel the top executives from Purdue Pharmaceutical, the Joint Commission, Press Ganey, and CMS and hospital administrators to appear and testify as to their role in this national epidemic. Blame must be placed; it is the American way.

**State of Wisconsin
Department of Safety & Professional Services**

AGENDA REQUEST FORM

1) Name and Title of Person Submitting the Request: Dale Kleven Administrative Rules Coordinator		2) Date When Request Submitted: 4/7/16 Items will be considered late if submitted after 12:00 p.m. on the deadline date: ▪ 8 business days before the meeting	
3) Name of Board, Committee, Council, Sections: Controlled Substances Committee of the Medical Examining Board			
4) Meeting Date: 4/20/16	5) Attachments: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	6) How should the item be titled on the agenda page? Legislation and Rule Matters – Discussion and Consideration 1. Proposals for Med 13 Relating to Continuing Medical Education for Prescribing Opioids	
7) Place Item in: <input checked="" type="checkbox"/> Open Session <input type="checkbox"/> Closed Session <input type="checkbox"/> Both	8) Is an appearance before the Board being scheduled? <input type="checkbox"/> Yes (Fill out Board Appearance Request) <input checked="" type="checkbox"/> No	9) Name of Case Advisor(s), if required:	
10) Describe the issue and action that should be addressed: 			
11) <i>Dale Kleven</i> <hr/> Signature of person making this request		Authorization <i>April 7, 2016</i> <hr/> Date	
<hr/> Supervisor (if required)		<hr/> Date	
<hr/> Executive Director signature (indicates approval to add post agenda deadline item to agenda) Date			
Directions for including supporting documents: 1. This form should be attached to any documents submitted to the agenda. 2. Post Agenda Deadline items must be authorized by a Supervisor and the Policy Development Executive Director. 3. If necessary, Provide original documents needing Board Chairperson signature to the Bureau Assistant prior to the start of a meeting.			

Chapter Med 13

CONTINUING MEDICAL EDUCATION FOR PHYSICIANS

Med 13.01 Authority and purpose.
 Med 13.02 Continuing medical education required; waiver.
 Med 13.03 Acceptable continuing medical educational programs.

Med 13.04 Physician postgraduate training program; length of service.
 Med 13.05 Evidence of compliance.
 Med 13.06 Audit.

Med 13.01 Authority and purpose. The rules in this chapter are adopted by the medical examining board pursuant to the authority delegated by ss. 15.08 (5) (b), 227.11 (2) and 448.13, Stats., and govern the biennial training requirements for physicians as provided under s. 448.13, Stats.

History: Cr. Register, February, 1977, No. 254, eff. 3-1-77; am. Register, March, 1979, No. 279, eff. 4-1-79; correction made under s. 13.93 (2m) (b) 7., Stats., Register, May, 1989, No. 401; am. Register, May, 1997, No. 497, eff. 6-1-97; am. Register, December, 1999, No. 528, eff. 1-1-00.

Med 13.02 Continuing medical education required; waiver. (1) Each physician required to complete the biennial training requirements provided under s. 448.13, Stats., shall, in each second year at the time of making application for a certificate of registration as required under s. 448.07, Stats., sign a statement on the application for registration certifying that the physician has completed at least 30 hours of acceptable continuing medical educational programs within the 2 calendar years immediately preceding the calendar year for which application for registration is made.

(2) A physician may apply to the board for waiver of the requirements of this chapter on grounds of prolonged illness or disability or other similar circumstances, and each case will be considered individually on its merits by the board.

History: Cr. Register, February, 1977, No. 254, eff. 3-1-77; am. (1), Register, March, 1979, No. 279, eff. 4-1-79; am. (1), February, 1981, No. 302, eff. 3-1-81; am. Register, May, 1997, No. 497, eff. 6-1-97; am. Register, December, 1999, No. 528, eff. 1-1-00.

Med 13.03 Acceptable continuing medical educational programs. The board shall accept the following in satisfaction of the biennial training requirement provided under s. 448.13, Stats.:

(1) (a) *Program approval.* Educational courses and programs approved in advance by the board may be used for credit, except that the board may approve for credit completed programs and courses conducted in other countries.

(b) *Physicians.* The board recognizes only those educational programs recognized as approved at the time of the physician's attendance by the council on medical education of the American medical association, or the American osteopathic association, or the accreditation council for continuing medical education or may recognize program providers outside the United States unless any of the foregoing have been previously disapproved by the board. The board will accept attendance at and completion of programs accredited as the American medical association's or the American osteopathic association's "Category I" or an equivalent as fulfilling the requirements of this chapter for continuing medical education. One clock hour of attendance shall be deemed to equal one hour of acceptable continuing medical education.

(2) (a) The board shall accept for continuing medical education credit, voluntary, uncompensated services provided by physicians specializing in psychiatry in assisting the department of health services in the evaluation of community outpatient mental health programs, as defined in s. 51.01 (3n), Stats., and approved by the department of health services according to rules promulgated under s. 51.42 (7) (b), Stats. Four hours of assistance, including hours expended in necessary training by the department

of health services, shall be deemed to equal one hour of acceptable continuing medical education for the purposes of this chapter.

(b) Physicians wishing to apply for continuing medical education credit under this subsection shall register in advance with the board and shall notify the board on forms provided by the board of the dates and the total number of hours in any biennium for which the applicant will be available to provide assistance. Referrals shall be made to the department of health services in the order received pursuant to requests for assistance received from that department by the medical examining board and by the psychology examining board.

Note: Forms are available upon request to the board office located at 1400 East Washington Avenue, P.O. Box 8935, Madison, Wisconsin 53708.

History: Cr. Register, February, 1977, No. 254, eff. 3-1-77; am. Register, February, 1981, No. 302, eff. 3-1-81; renum. Med 13.03 to be 13.03 (1) and am., cr. (intro.), (2), Register, November, 1995, No. 479, eff. 12-1-95; r. and recr. (1), Register, May, 1997, No. 497, eff. 6-1-97; r. (1) (c), Register, December, 1999, No. 528, eff. 1-1-00; correction in (2) made under s. 13.92 (4) (b) 6., Stats., Register November 2011 No. 671.

Med 13.04 Physician postgraduate training program; length of service. The board will accept postgraduate training in a program approved by the board under the provisions of s. Med 1.02 (3), as fulfilling the requirements of this chapter for continuing medical education for physicians. Three consecutive months of such postgraduate training shall be deemed to equal 30 hours of acceptable continuing medical education for the purposes of this chapter.

History: Cr. Register, February, 1977, No. 254, eff. 3-1-77; am. Register, March, 1979, No. 279, eff. 4-1-79; am. Register, May, 1997, No. 497, eff. 6-1-97.

Med 13.05 Evidence of compliance. (1) PHYSICIANS. The board will accept as evidence of compliance by physicians with the requirements of this chapter, as original documents or verified copies thereof, any or all or any combination of the following:

(a) Certification by either the providing institution or organization or the American medical association or the American osteopathic association, or components thereof, of attendance at and completion of continuing medical education programs approved under the provisions of s. Med 13.03 (1) (a).

(b) A "Physician's Recognition Award" of the American medical association or a certificate of continuing medical education from the American academy of family physicians awarded not more than 12 months prior to the beginning of the calendar year for which application for registration is being made.

(c) Certification by a chief of service or head of department or director of medical education of the providing facility of appointment to and satisfactory participation in a postgraduate training program approved under the provisions of s. Med 13.04.

(2) **RETENTION REQUIREMENT.** Evidence of compliance shall be retained by each physician through the biennium for which 30 hours of credit are required for registration.

History: Cr. Register, February, 1977, No. 254, eff. 3-1-77; am. (1) (intro.) and r. and recr. (2), Register, February, 1981, No. 302, eff. 3-1-81; am. (1) (intro.), (a) and (2), cr. (1m), Register, May, 1997, No. 497, eff. 6-1-97; r. (1m), am. (2), Register, December, 1999, No. 528, eff. 1-1-00.

Med 13.06 Audit. The board shall conduct a random audit of licensees on a biennial basis for compliance with the continuing

education requirement stated in s. [Med 13.02 \(1\)](#). The board may require any physician to submit evidence of compliance with the continuing education requirement to the board during the biennium for which 30 hours of credit are required for registration to audit compliance.

History: Cr. [Register, February, 1981, No. 302, eff. 3-1-81](#); am. [Register, May, 1997, No. 497, eff. 6-1-97](#); am. [Register, December, 1999, No. 528, eff. 1-1-00](#); [CR 14-033](#); am. [Register May 2015 No. 713, eff. 6-1-15](#).