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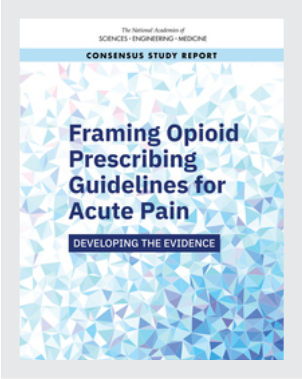

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Framing Opioid Prescribing Guidelines for Acute Pain

DEVELOPING THE EVIDENCE

Committee on Evidence-Based Clinical Practice Guidelines
for Prescribing Opioids for Acute Pain

Board on Health Care Services

Health and Medicine Division

A Consensus Study Report of
The National Academies of
SCIENCES • ENGINEERING • MEDICINE

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COMMITTEE ON EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES FOR PRESCRIBING OPIOIDS FOR ACUTE PAIN

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **KENNETH W. KIZER,** Atlas Research, and **LINDA C. DEGUTIS,** Henry M. Jackson Foundation. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

In Memoriam

This Consensus Study Report is dedicated to Dr. Richard Payne, an international expert in palliative care and pain management, a valued member of the committee, and an irreplaceable friend and colleague.

Preface

If readers look in their medicine cabinets, it is likely many will find prescription opioids left over from a previous acute pain episode. The treating clinician likely wanted to err on the side of providing adequate pain relief. But from an individual and a public health perspective, these leftover opioid pills may lead to long-term use, opioid use disorder, and unintentional overdoses among patients and others if taken by people for whom the pills were not prescribed. The committee believes that the need both to alleviate severe acute pain and to reduce public health harms make this report important for a broad audience, including clinicians and other health care providers, patients, and the public.

How might this report be useful? Evidence on opioid use, patient outcomes, and adverse effects for patients and the public health is being published continuously. This report offers a framework for evaluating that evidence to support a clinical practice guideline, recommends acute pain indications where better practice guidelines might affect public health, and points out evidence gaps that need to be filled with future research. Both acute pain and opioid use disorder and overdose can cause distress to patients and their communities; emotions on these topics run high. This report points the way to how rigorous evidence and guidelines based on that evidence can reduce inappropriate opioid prescribing for acute pain and thereby help prevent further distress.

On behalf of the committee, I would like to express our sincere gratitude to the many individuals and groups who provided valuable information and insights to assist the committee with its deliberations. In particular, we would like to thank the representatives of the U.S. Food and Drug Administration: Scott Gottlieb, Judy Staffa, and Douglas Throckmorton. The following individuals also participated in the committee's workshops: Richard Barth, Jr., Dartmouth-Hitchcock Medical Center; Brian Bateman, Brigham and Women's Hospital; Leslie Bisson, University at Buffalo; Kevin Bozic, The University of Texas at Austin Dell Medical School; Steven Brown, University of Arizona College of Medicine; Benjamin Friedman, Albert Einstein College of Medicine; David Goldfarb, New York University School of Medicine; Elizabeth Habermann, Mayo Clinic; Elliot Hersh, University of Pennsylvania School of Dental Medicine; Debra Houry, Centers for Disease Control and Prevention (CDC); Ula Hwang, Icahn School of Medicine at Mount Sinai; David Jevsevar, Geisel School of Medicine at Dartmouth; Clifford Ko, University of California, Los Angeles (UCLA), School of Medicine; Elliot Krane, Stanford University;

Lisa Leffert, Massachusetts General Hospital; Christina Mikosz, CDC; Paul Moore, University of Pittsburgh School of Dental Medicine; Douglas Owens, U.S. Preventive Services Task Force and Stanford University; Darshak Sanghavi, OptumLabs; Holger Schünemann, GRADE and McMaster University; Paul Shekelle, UCLA School of Medicine; Wally Smith, Virginia Commonwealth University; and Joanna Starrels, Albert Einstein College of Medicine.

We would also like to thank the following individuals for conducting data analyses for the committee: Jill Ashman, Carol DeFrances, Pinyao Rui, Susan Schappert, and Brian Ward from CDC, and Brian Bateman from Brigham and Women's Hospital. We also appreciate the materials sent by other interested parties, including several medical specialty societies.

As chair, I also want to thank my colleagues on the committee for their hard work, willingness to reconsider their views in the light of evidence and other perspectives, and their collegiality. I also want to acknowledge the contributions of Mark Bicket, M.D., and Eric Sun, M.D., Ph.D., who stepped off the committee when they started full-time positions with the federal government. I also want to remember Richard Payne, M.D., who died shortly after resigning from the committee, for his career-long dedication to relieving the suffering of patients living with pain and his commitment to reducing health disparities.

Finally, the committee's report would not have been possible without the expertise, dedication, and hard work of the National Academies' staff: Roberta Wedge, Cyndi Trang, Ruth Cooper, Daniel Bearss, and Rebecca Morgan. The committee gratefully thanks them.

Bernard Lo, *Chair*
Committee on Evidence-Based Clinical Practice Guidelines for Prescribing Opioids for Acute Pain

Contents

Acronyms and Abbreviations

AAAPT	ACTTION–APS–AAPM Pain Taxonomy
AAN	American Academy of Neurology
AAOMS	American Association of Oral and Maxillofacial Surgeons
AAOS	American Academy of Orthopaedic Surgeons
AAPD	American Academy of Pediatric Dentistry
AAPM	American Academy of Pain Medicine
ACOEM	American College of Occupational and Environmental Medicine
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ACTTION	Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks
ADA	American Dental Association
AGREE	Appraisal of Guidelines, Research and Evaluation
AHIP	America's Health Insurance Plans
AHRQ	Agency for Healthcare Research and Quality
AHS	American Headache Society
APS	American Pain Society
ASIPP	American Society of Interventional Pain Physicians
AUA	American Urological Association
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMSS	Council of Medical Specialty Societies
CORE	Center for Opioid Research and Education
CPG	clinical practice guideline

DoD	U.S. Department of Defense
DSM-5	*Diagnostic and Statistical Manual for Mental Disorders, 5th Edition*
EAU	European Association of Urology
ED	emergency department
EHC	Effective Health Care program
EHR	electronic health record
FDA	U.S. Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IOM	Institute of Medicine
IQR	interquartile range
MHA	Massachusetts Health & Hospital Association
MME	morphine milligram equivalent
NAMCS	National Ambulatory Medical Care Survey
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHLBI	National Heart, Lung, and Blood Institute
NSAID	nonsteroidal anti-inflammatory drug
OME	oral morphine equivalent
OPEN	Opioid Prescribing Engagement Network
OR	odds ratio
PDMP	prescription drug monitoring program
PICOTS	patient, problem, or population; intervention; comparison, control, or comparator; outcome; time; and setting
QI	quality improvement
RCT	randomized controlled trial
SCD	sickle cell disease
THA	total hip arthroplasty
TKA	total knee arthroplasty
USPSTF	U.S. Preventive Services Task Force
VA	U.S. Department of Veterans Affairs
VOC	vaso-occlusive crisis
WHO	World Health Organization

Summary

Opioids have long been prescribed to relieve pain. Acute pain can often be treated and relieved by nonopioid and nonpharmacologic approaches. However, when acute pain is severe or does not respond to other treatments, opioids can provide effective relief.

In the United States opioid prescribing increased steadily from 1999 to 2010, but has decreased modestly since 2012. In spite of the decrease in opioid prescribing, the number of deaths from opioid overdoses, which began to increase noticeably in 1999, has continued to rise, resulting in the ongoing opioid overdose epidemic.

In 2017, 17% of the U.S. population received at least one opioid prescription. To put U.S. prescribing practices for acute pain into context, U.S. dentists prescribe opioids at rates 37[1] times greater than dentists in the United Kingdom, and U.S. patients undergoing minor surgeries are prescribed opioids 76% of the time compared with 11% of the time in Sweden.

Opioids pose risks not only to patients for whom they are prescribed, but also to family members and the community. Between 6% and 14% of opioid-naïve patients receiving an opioid prescription for pain in the emergency department (ED) or postoperatively continue to use opioids 6–12 months after the initial prescription, and a large number of pills being supplied in the initial prescription is associated with a higher rate of prolonged or high-risk use. However, between 41% and 72% of patients do not use all of the opioids they are prescribed postoperatively. These unused opioids can be misused by the patient and others, particularly family members. There is an association between opioid prescriptions to patients and opioid overdose among family members, particularly among children and adolescents. Finally, most heroin users report misusing prescription opioids prior to initiating heroin use.

The opioid overdose epidemic combined with the need to reduce the burden of acute pain poses a public health challenge. To address how evidence-based clinical practice guidelines (CPGs) for prescribing opioids for acute pain might help meet this challenge, the U.S. Food and Drug Administration (FDA) asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to establish a committee to conduct the tasks given in Box S-1.

[1] This text has been revised since prepublication release.

BOX S-1
Statement of Task

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will develop a framework to evaluate existing clinical practice guidelines for prescribing opioids for acute pain indications, recommend indications for which new evidence-based guidelines should be developed, and recommend a future research agenda to inform and enable specialty organizations to develop and disseminate evidence-based clinical practice guidelines for prescribing opioids to treat acute pain indications.

In developing its report, the committee will:

- Identify existing opioid prescribing guidelines for acute pain indications;
- Identify a list of specific medical procedures and conditions associated with acute pain (i.e., develop a prioritized list not to exceed 50) for which opioids are commonly prescribed and for which evidence-based clinical practice guidelines would thus help inform prescribing practices. This list should be prioritized to identify those first which are deemed to have the greatest potential impact on public health;
- Develop a framework for evaluating the evidence base underpinning clinical practice guidelines for opioid prescribing to create a threshold level of evidence to support guidelines and ensure consistency among guidelines;
- Evaluate existing opioid prescribing guidelines for acute pain using this framework to identify specific indications for which prescribing guidelines are not sufficiently evidence-based; and
- Develop a prioritized research agenda, by specific medical procedure or condition (not to exceed 10 of each surgical procedure or medical condition) for which no opioid prescribing guidelines exist or for which more evidence is required to support existing guidelines, to enable the development and availability of comprehensive evidence-based opioid prescribing guidelines for acute pain.

In developing its evaluation framework, the committee will consider the standards established in the 2011 Institute of Medicine report *Clinical Practice Guidelines We Can Trust*. The committee will produce recommendations for how to generate easily accessible, evidence-based, trustworthy clinical practice guidelines for effectively managing acute pain with opioid drugs for specific medical procedures and conditions that the U.S. Food and Drug Administration could use as a reference in its publicly available materials.

COMMITTEE'S APPROACH

To accomplish FDA's tasks, the National Academies empaneled a committee of 15 experts who had experience in the development and use of CPGs. The committee recognized that the audience for its report would include not only FDA and other governmental agencies at the federal, state, and local levels, but also professional societies, health care organizations, and health insurers who have developed or may develop guidelines for opioid prescribing. Finally, the committee recognized that individual health care providers, as well as patients, their caregivers, and their communities, all have an interest in optimal prescribing of opioids, not only to manage the patients' acute pain, but also to prevent opioids from harming them and others. At the request of FDA, the committee focused on opioid prescribing in outpatient settings or at discharge following inpatient care.

The committee held five meetings, three of which included public sessions. At the first meeting, the committee heard from several FDA representatives, a representative of the Centers for Disease Control and Prevention (CDC), and the general public. At the two following public sessions, subject matter experts presented their views on what surgical procedures and medical conditions are associated with acute pain for which opioid analgesics are prescribed as well as on priorities for a research agenda on medical conditions and surgical procedures (collectively called "indications") for which no clinical guidelines exist or for which more evidence is required to support existing guidelines.

The committee also conducted literature searches to identify current opioid prescribing practices and trends, existing opioid prescribing guidance, the use of opioids to treat acute pain for selected medical and surgical indications, information on the prevalence and incidence of those selected indications, and standards for CPGs.

MANAGING ACUTE PAIN

The committee's definition of "acute pain" was derived from multiple authoritative sources (e.g., CDC, the U.S. Department of Health and Human Services' National Pain Strategy, the ACTTION–APS–AAPM Pain Taxonomy Classification of Acute Pain Conditions, and the Institute of Medicine[2]). Acute pain is often characterized as not being chronic pain; the latter is almost always considered to be pain that lasts 3 months or longer. Pain that lasts longer than 30 days but less than 90 days is often referred to as subacute pain and represents a transition between acute and chronic pain. The committee determined that for this report, acute pain was the sudden onset of pain that lasts no longer than 90 days.

Acute pain causes physical and emotional distress, affecting a person's quality of life, sleep, physical functioning, mental health, and ability to meet family, job, school, and other responsibilities. Suboptimal pain management can increase morbidity, slow recovery, prolong analgesic use during and after hospitalization, and increase the cost of care.

Acute pain is common in a number of health care settings. In primary care, back, neck, and joint pain, musculoskeletal injury, and headache are among the most common patient complaints. In EDs the principal reason for more than 20% of visits is some form of pain. Among patients who undergo surgery, approximately 80% report postsurgical pain, and 88% of those patients experience moderate to extreme pain.

Numerous patient, population, and clinician factors influence the presentation and treatment of acute pain as well as a clinician's decision whether to prescribe opioids. These factors include the patient's age, sex, and health literacy as well as the presence or absence of comorbidities. There are various health disparities associated with opioid prescribing for acute pain; people of color may be less likely to have access to or be prescribed opioids for their pain. Genetic variations in how people metabolize opioids may also affect their response to treatment.

THE USE AND DEVELOPMENT OF CLINICAL PRACTICE GUIDELINES

Current Availability of Clinical Practice Guidelines

Numerous organizations, ranging from professional societies, federal agencies, and state and local governments to individual health care organizations and departments, have implemented some form

[2] As of March 2016, the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM). The IOM name is used to refer to publications issued prior to July 2015.

of opioid prescribing guidelines. For example, opioid prescribing guidelines have been promulgated by the American Academy of Emergency Medicine and the American College of Occupational and Environmental Medicine (ACOEM). All 50 states and the District of Columbia have some form of opioid prescribing guidelines, which can range from advisory guidelines to legally binding limits on opioid prescribing. Some municipalities, such as New York City and Philadelphia, also have recommendations for opioid prescribing in EDs. Guidelines vary from a short list of prescription recommendations for number and dose of opioids to evidence-based CPGs developed by professional societies (e.g., Society for Pediatric Anesthesia) and federal agencies (e.g., the 2016 CDC *Guideline for Prescribing Opioids for Chronic Pain*). Some states mandate that prescription drug monitoring programs be used by providers to access a patient's history of prescription opioids and require that prescribers complete some form of mandatory education.

Trustworthy guidelines help clinicians translate current research in basic science and diagnostic and therapeutic interventions into clinical practice, with the goal of improving patient health and societal outcomes. CPGs provide clinicians with recommendations for treatment based on the best available, up-to-date evidence. CPGs may also address treatments for specific subpopulations, such as patients with physical or mental comorbidities, children or the elderly, patients who are currently are taking opioids for a chronic condition, and patients with a substance use disorder.

Despite the recognized merits of CPGs, they also have limitations, including a lack of evidence on which to develop prescribing recommendations; a lack of evidence to inform individualization of therapy based on patient, setting, clinician, and other factors; and slow uptake by clinicians and policy makers. CPGs may be misinterpreted or result in unintended consequences. For example, the 2016 CDC guideline on opioids for chronic pain was inappropriately used to support policies by other organizations for mandatory opioid tapering when the guideline specifically stated that this was not its purpose. Finally, new evidence can make CPGs outdated.

As described in the 2011 IOM report *Clinical Practice Guidelines We Can Trust*, standardized, transparent methodologies are more likely to produce trustworthy, evidence-based, and accepted CPGs. Several organizations, including the IOM, the U.S. Preventive Services Task Force, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, the Appraisal of Guidelines, Research and Evaluation Collaborative, the U.S. Department of Veterans Affairs in collaboration with the U.S. Department of Defense, and the UK National Institute for Health and Care Excellence, have published methodologies for establishing rigorous approaches to the development of guidelines. Many medical and health care professional societies also have standardized methods for producing CPGs, such as the American Academy of Family Physicians, the Council of Medical Specialty Societies, and ACOEM.

Frameworks for Clinical Practice Guidelines

The development of CPGs is based on three core principles: (1) guidelines should be based on evidence that evaluates the efficacy or effectiveness of interventions on health outcomes; (2) guidelines should use the highest-quality evidence available; and (3) guidelines by their nature are developed for application to populations of patients, but should allow for individualization of care to the extent possible. High-quality CPGs are based on a guideline development process that begins with identifying the need for recommendations for a specific surgical or medical indication and proceeds through the selection of guideline developers, gathering and evaluating the scientific evidence, approving the guideline, disseminating the guideline, monitoring its use, and, finally, revising it in a continuous quality improvement context. The committee's CPG development approach provides a stepped process (see Figure S-1) for assessing the available evidence on opioid prescribing for acute pain indications,

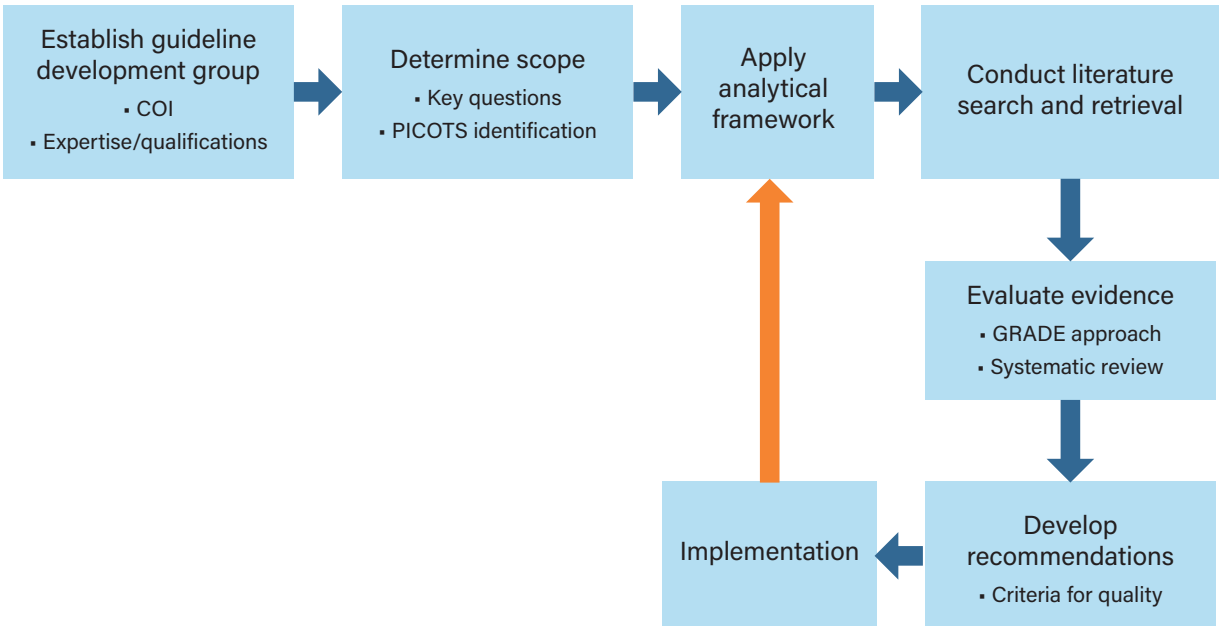

FIGURE S-1 The evidence-based clinical practice guideline (CPG) development process. The orange arrow indicates where monitoring and assessment informs re-evaluation of the guideline and informs the feedback loop to periodically update the CPG as new evidence becomes available.
NOTE: COI=conflict of interest; GRADE=Grading of Recommendations Assessment, Development and Evaluation; PICOTS=patient, problem, or population; intervention; comparison, control, or comparator; outcome; time; and setting.

identifying research needs, and facilitating the incorporation of new knowledge into clinical practice as it becomes available.

Establishing a Guideline Development Group

A guideline development group that includes experts and representatives of key stakeholders and health care providers as well as methodologists, epidemiologists, and statisticians will strengthen the rigor and applicability of evidence-based CPGs. Diversity among the guideline developers with regard to expertise, experience, and geographic location is desirable, and the incorporation of the patient perspective will help support the goal of patient-centered care.

Reducing the susceptibility of guideline development groups to conflicts of interest through the use of established, detailed procedures for assessing and managing both financial and non-financial conflicts is essential. Once potential group members have been identified, any conflicts of interest may be posted publicly to enhance transparency.

Scoping the Guideline

The first task of the CPG development group is to delineate which surgical or medical indications the CPG will cover via the statement of scope and setting (e.g., interventions to be assessed and patient populations). The statement is based on a clear description of the patient, problem, or population (P);

intervention (I); comparison, control, or comparator (C); outcome (O); time (T); and setting (S)—the PICOTS process. The PICOTS process helps to define the scope of the guideline, develop the key questions to be addressed by the systematic literature reviews, identify the relevant literature, and inform the evidence evaluation process. Health equity issues for various populations and indications may also be considered in the statement of scope.

Analytic Framework

The analytic framework recommended by the committee in Figure S-2 identifies the evidence linkages to be evaluated in a systematic review of the effects of an intervention on health outcomes. The analytic framework visually depicts the evidence and potential data gaps that need to be assessed to make a recommendation on opioid prescribing in order to achieve the best possible health outcomes (see rightmost box of Figure S-2), the intermediate outcomes that are associated with those health outcomes, and the linkages between intermediate and health outcomes. The analytic framework indicates the key questions to be answered by the evidence, typically using a PICOTS approach. Examples of key questions include in patients with acute pain requiring opioid therapy, what is the comparative effectiveness of different opioid prescribing strategies on intermediate outcomes (e.g., refill requests, unused pills, misuse, or diversion)? And in patients with acute pain, what is the association between decreased opioid use and health outcomes?

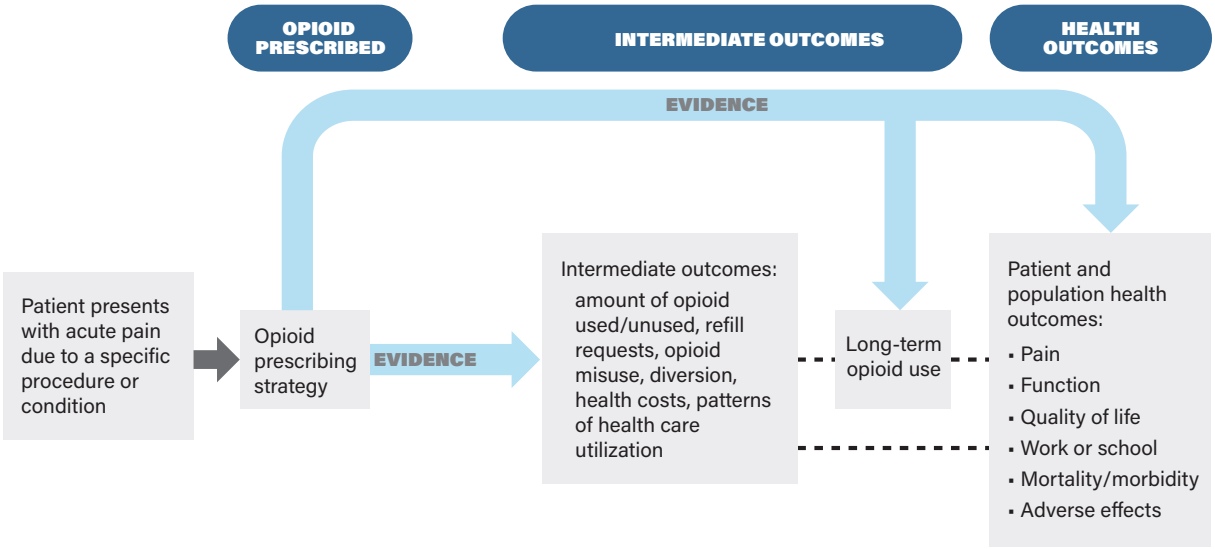

FIGURE S-2 Analytic framework for prescribing opioids for acute pain. This figure shows the evidence linkages that are necessary to support the development of a clinical practice guideline for opioid prescribing. The framework begins with a determination of the patient population that is presenting with acute pain (e.g., opioid-naïve patients versus opioid exposed). The wide arrow indicates evidence evaluating the effects of an opioid prescribing strategy on a health or intermediate outcome. The dotted lines indicate linkages between different outcomes (e.g., the association between a lesser amount of opioid used and risk of long-term use or quality of life), not between an intervention and an outcome (or, in the case of intermediate outcomes and long-term opioid use, between one intermediate and another intermediate outcome). Short- and long-term health outcomes, both beneficial and harmful, may be seen at the patient and community or population levels.

Defining the outcomes and showing the evidence linkages provides a structured framework by which CPG developers can assess the benefits and drawbacks of different opioid prescribing strategies. The framework is based on the principles that interventions should improve health outcomes, not just intermediate outcomes, and that evaluations of interventions should be based on assessments of both benefits and harms. The patient populations to be studied for a given prescribing strategy are defined during the scoping progress. Prescribing strategies may be based on the characteristics of the patient population, including the indication for pain (e.g., underlying medical condition or surgical procedure), demographic factors (e.g., age, sex, race/ethnicity), clinical factors (e.g., the presence of chronic pain, prior opioid use, use of other interventions, substance use history, and mental and physical comorbidities), and practice setting (e.g., primary care, inpatient, ED).

The prescribing strategies in the analytic framework are compared across comparable populations with the same acute pain indication. For example, opioid prescribing strategies may compare the effectiveness of variations in the amount of opioids prescribed (e.g., for 3 or 7 days, or a dose of 20 morphine milligram equivalents [MMEs][3] versus 40 MMEs) for a particular indication (e.g., low back pain) or population (e.g., children or the elderly). The prescribing strategies can take into account the specific opioid used, dosing frequency, mechanism of action, mode of delivery, and other factors.

Intermediate outcomes for opioid prescribing strategies at the patient and health care system levels include markers such as the amount of opioids used and unused and refill requests. Individuals who use greater amounts of opioids may increase their risk of adverse health outcomes, such as overdose, and increase the likelihood of long-term use. Long-term use, an intermediate outcome, does not directly measure effects on patient morbidity, mortality, or other health outcomes, but may be associated with these or other long-term adverse health consequences.

A comprehensive assessment of health outcomes takes into account short- and long-term outcomes for the individual patients with acute pain and for the communities or populations to which they belong. Health outcomes to be assessed include pain relief, improved quality of life, improved social and physical function, decreased adverse effects, and increased mortality.

The committee makes the following recommendations regarding the development of a framework to evaluate evidence-based CPGs:

Recommendation: Professional societies; health care organizations; local, regional, and national stakeholders; and other developers of evidence-based clinical practice guidelines (CPGs) for opioid prescribing for acute pain should use an analytic framework (e.g., Figure S-2) to develop and assess the evidence base for each CPG. The opioid prescribing strategies, intermediate outcomes, and health outcomes evaluated to develop the CPG should be explicitly described. CPGs should use a well-accepted methodology (e.g., the Grading of Recommendations Assessment, Development and Evaluation [GRADE] approach) for grading the evidence and rating the strength of the recommendations.

Recommendation: Developers of evidence-based clinical practice guidelines (CPGs) for outpatient opioid prescribing for acute pain indications should explicitly state the patient populations to which the CPG is applicable (e.g., adults versus children), and those subpopulations for whom the CPG recommendations may need to be modified such as, for

[3] MMEs are used to standardize reporting of the dose of opioids a person receives across different opioids. For example, 50 MMEs per day is equal to 50 mg of hydrocodone (10 pills of hydrocodone/acetaminophen 5/300) or 33 mg of oxycodone (approximately two 15 mg pills of sustained-release oxycodone). See https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf (accessed September 18, 2019).

example, patients with comorbidities, prior opioid exposure, or opioid use disorder. CPG developers should also explicitly define the contextual aspects of prescribing, such as setting, prescriber type, and prior treatments.

Recommendation: Researchers should specify opioid prescribing strategies in a standardized manner, including the drug, strength, amount, and duration of the opioids. Reporting opioid prescriptions as morphine milligram equivalents (MMEs) would facilitate evaluation of different opioids based on analgesic potency.

Evidence Evaluation Framework

The evidence evaluation framework is a process by which CPG developers may assess the evidence indicated by the linkages in Figure S-2. Such evaluations can be used to determine the strength of recommendations for an effective opioid prescribing strategy. CPGs consider all types of evidence to assess the linkages between specific opioid prescribing strategies and intermediate and health outcomes in patients with acute pain. Randomized controlled trials (RCTs), observational studies, and quality improvement initiatives may all provide evidence for linkages in the analytic framework. Expert opinion and consensus statements may be included in CPGs, but are usually considered the weakest form of evidence.

Systematic reviews and meta-analyses are methods to summarize and synthesize a body of literature that may include RCTs or observational studies or both. The use of systematic review methods reduces bias in how studies are selected and analyzed.

Although several organizations have developed formal methods to evaluate the evidence base for clinical questions, the committee found GRADE to be the most useful. This standardized and systematic approach grades the quality of evidence (indicating certainty in findings) and rates the strength of recommendations based on that evidence. GRADE rates the quality of the body of evidence using the following criteria: risk of bias, publication bias, imprecision (random error), inconsistency, indirectness, rating up the quality of evidence, and resource use. In the GRADE approach, study limitations that decrease confidence in the findings include a lack of allocation concealment, a lack of blinding, incomplete accounting of patients and outcome events, selective outcome reporting bias, stopping early for benefit, use of invalidated outcome measures (e.g., patient-reported outcomes), carryover effects in crossover trials, and recruitment bias in cluster-randomized trials.

Evaluating and reporting the strength of evidence is critical for developing CPGs, so that readers can determine how confident they should be in the recommendations. GRADE methodology also addresses factors such as the magnitude of benefits relative to harms, costs, values and preferences, feasibility and implementability, and equity. CPG developers can evaluate the evidence for each of the linkages in the analytic framework using the GRADE criteria and evaluate whether a prescribing strategy is associated with benefits (e.g., decreased overdoses) that outweigh the harms (e.g., a slight increase in average pain). Assessing the balance of benefits to harms requires a consideration of how health outcomes have been prioritized during the earlier scoping step. If the evidence does not support the linkages from a prescribing strategy to an improved health outcome (directly or indirectly), then the CPG developers may opt to either not make a recommendation or make a recommendation but be very explicit about the low quality of the supporting evidence. When the evidence for a linkage is weak but there is little risk of harm and a high likelihood of benefit, a strong recommendation could be formulated based on weak evidence. Such a recommendation may be appropriate to reduce the likelihood of serious harms when there is evidence

of little impact on effectiveness; this has been done in the acute pain context to avoid adverse effects of opioids when there is evidence that opioids are not superior to nonopioid pharmaceuticals.

Recommendation: Researchers who conduct studies to determine optimal opioid prescribing strategies for acute pain should examine not only the intermediate outcomes (e.g., pills prescribed and unused and long-term opioid use), but also the short- and long-term health outcomes (e.g., mortality, overdose, opioid use disorder, pain, and function) at both the patient and population levels.

Recommendation: Researchers studying opioid prescribing for acute pain should address evidence gaps by linking opioid prescribing strategies to health outcomes using appropriate study designs. Well-designed observational and quality improvement initiatives are helpful for evaluating the effects of opioid prescribing strategies on health outcomes.

Implementation

After recommendations for opioid prescribing strategies have been developed and approved, consideration needs to be given to ensuring the effective dissemination, uptake, impact, and periodic revisions of the CPG, all of which are activities that are part of implementation. Many organizations that develop CPGs already have mechanisms in place to disseminate them to appropriate audiences. For example, members of a medical specialty society may learn about a new or changes to an existing CPG at annual or regional meetings, at continuing medical education activities, or from educational materials from state medical boards. Implementation also addresses how CPGs relate to different clinical practice and clinical settings, how to increase the applicability and impact of guidelines, and how to evaluate the impact of the guideline on health outcomes. A critical aspect of CPG implementation is the need for continuous quality improvement, including audit and feedback. As each CPG is disseminated and applied in clinical practice, outcome data need to be gathered at the patient and community levels to ensure the appropriate uptake and evaluation of the intended and possible unintended effects. Such information can assist guideline developers in revising and updating the CPG when necessary so that it reflects the most current evidence available to ensure that patients with acute pain receive the best care.

Recommendation: Organizations that develop evidence-based clinical practice guidelines (CPGs) on opioid prescribing for acute pain, including governmental entities (federal, state, and local) and nongovernmental entities, such as professional societies, health care organizations and collaboratives, and health insurers, should establish a process for disseminating, implementing, and monitoring the uptake and impacts of the CPG on opioid prescribing practices. These impacts include short- and long-term patient and population-level intermediate and health outcomes, particularly opioid misuse, opioid use disorder, and opioid overdoses and deaths.

PRIORITIZING SURGICAL AND MEDICAL INDICATIONS FOR CLINICAL PRACTICE GUIDELINE DEVELOPMENT

The National Academies committee was tasked with identifying and prioritizing up to 50 specific surgical procedures and medical conditions that are associated with acute pain and for which opioid analgesics are commonly prescribed and considered clinically necessary. The committee was also tasked

with recommending where evidence-based CPGs would have the greatest impact on public health. The committee determined that a priority indication would meet three criteria: the prevalence of the surgical or medical indication was high; there was evidence of variation in opioid prescribing in relation to patient-centered or patient-reported outcomes; and an evidence-based CPG or other guidance on opioid prescribing for acute pain associated with the indication was available for review.

The committee began developing its list of priority surgical and medical indications by conducting literature searches to identify the most prevalent indications associated with acute pain and opioid prescribing. The committee also identified specific indications associated with acute pain for which some type of guidelines have been published or for which CPGs would be helpful but no guidelines currently exist according to literature searches, input from experts at its public sessions, and the committee's expertise. There were few guidelines that were specific for (1) opioids, (2) acute pain, and (3) a specific indication, but there are several guidelines that met at least two of those criteria.

Given the heterogeneity of the potential indications for acute pain, the committee did not create a standardized algorithm for prioritizing the creation of CPGs for opioid prescribing for acute pain. The committee considered that there are many acute pain conditions for which CPGs may be appropriate and that stakeholders might vary in how they prioritize these and other conditions depending on a number of factors such as emerging science or great variability in opioid prescribing.

The committee deemed the surgical and medical indications in Table S-1 to be priorities for the development of evidence-based CPGs or, if a guideline was already available, as a candidate for modifying the guideline or strengthening the evidence base to meet the standards in the committee's analytic framework.

Recommendation: Professional societies, health insurers, and health care organizations should consider the prioritized surgical and medical indications listed in Table S-1 for evidence-based clinical practice guideline (CPG) development or, where a CPG already exists, for modification to meet the analytic and evidence frameworks in this report. The committee acknowledges that other surgical and medical indications may emerge as priorities as the evidence base grows.

EVALUATING SELECTED CLINICAL PRACTICE GUIDELINES

The committee evaluated seven existing opioid prescribing guidelines for acute pain for selected indications against its analytic framework. It chose three surgical procedures and four medical conditions that have public health impacts, for which there were some type of available guidelines and some evidence regarding opioid prescribing, and that were different in scope and context. The three surgical procedures—cesarean and vaginal delivery, third molar extractions, and total knee replacement—and the four medical conditions—renal stones, migraine headaches, low back pain, and sickle cell disease—vary with regard to the affected populations, such as children, adolescents, adults, older populations, women of reproductive age, and minority populations. Evaluating the guidance chosen for each indication allowed the committee to identify data needs and research gaps for prescribing opioids for each indication.

The committee recognized that its task was predicated on the determination that opioids would be prescribed for acute pain for a given indication. In its review of the available guidance, the committee determined that many CPGs consider the use of opioids for pain control in the context of a broader multimodal approach to pain management (e.g., the CPG for low back pain developed by the American Pain Society) and that opioids are often not a recommended first-line treatment. In clinical practice the decision to use opioids for acute pain is often made in the context of a comprehensive treatment

TABLE S-1 Priority Indications for Acute Pain for Clinical Practice Guideline Development or Modification (listed alphabetically)

Surgical Indications	Medical Indications
Anorectal, pelvic floor, and urogynecologic (e.g., colon resection, hemorrhoidectomy, vaginal hysterectomy)	Dental pain (nonsurgical)
Breast procedures (e.g., lumpectomy, mastectomy, reconstruction, reduction)	Fractures
Dental surgeries (e.g., third molar extraction)	Low back pain (includes lumbago, dorsalgia, backache)
Extremity trauma requiring surgery (e.g., amputation, open reduction and internal fixation)	Migraine headache
Joint replacement (e.g., total hip arthroplasty, total knee arthroplasty)	Renal stones (also called kidney stones, nephrolithiasis, calculus of the kidney, renal colic)
Laparoscopic abdominal procedures (e.g., appendectomy, bariatric surgery, cholecystectomy, colectomy, hysterectomy, prostatectomy)	Sickle cell disease
Laparoscopic or open abdominal wall procedures (e.g., femoral hernia, incisional hernia, inguinal hernia)	Sprains/strains, musculoskeletal
Obstetric surgeries (e.g., cesarean delivery, vaginal delivery)	Tendonitis/bursitis
Open abdominal procedures (e.g., appendectomy, cholecystectomy, colectomy, hysterectomy)	
Oropharyngeal procedures (e.g., tonsillectomy)	
Spine procedures (e.g., fusion in both adults and children, laminectomy)	
Sports-related procedures (e.g., anterior cruciate ligament repair and reconstruction, joint arthroscopy, rotator cuff repair)	
Thoracic procedures (e.g., thoracoscopy, repair of pectus excavatum in children [Nuss procedure])	

plan tailored to an individual patient. Such treatment plans ideally consider the patient's health status, including pre-existing conditions, comorbidities, prior reactions to opioids or other pharmaceuticals, treatment preferences, and the availability of and access to all treatment modalities. However, it is difficult to determine the most effective opioid prescribing strategy because many studies that evaluate opioid prescribing fail to mention other interventions that may be prescribed by the clinician or used by the patient, including the use of over-the-counter medications and interventions such as acupuncture.

Recommendation: Developers of evidence-based clinical practice guidelines (CPGs) for an acute pain indication should address the appropriate use of opioids for the indication as well as the optimal opioid prescribing strategies. CPGs should explicitly state the role of opioid alternatives, such as acetaminophen or nonsteroidal anti-inflammatory drugs, as first-line therapies and the role and prescribing of opioids in the context of nonopioid pharmacologic and nonpharmacologic alternatives.

Researchers who evaluate opioid prescribing strategies for an acute pain indication should also specify any other interventions, including nonopioid interventions, used to relieve pain in the patient populations to be studied.

A RESEARCH AGENDA FOR OPIOID PRESCRIBING FOR ACUTE PAIN

The committee reviewed many studies that reported on the short- and long-term intermediate effects of reduced opioid prescribing in various health care systems, and several of these studies also reported on health outcomes in terms of patient reports of satisfaction with their care and pain control. However, there is a paucity of studies that examine the effects of opioid prescribing strategies on population-level outcomes such as fewer opioid overdoses seen in the ED, fewer first overdoses in which naloxone rescue therapy is needed, and fewer opioid-related deaths in the community. Although efforts to address the opioid epidemic are the impetus for many of the strategies to reduce inappropriate opioid prescribing, the societal impact of such strategies is not clearly understood and requires further research. While it seems intuitive that reducing opioid prescribing may result in fewer opioid overdoses and deaths, the impact of such reductions on patient pain control and the risk of unintended consequences for patients, their support systems, and their communities cannot be assumed and should be informed by accurate and comprehensive data.

To address these data gaps and support the development of more robust evidence-based CPGs, the committee makes the following recommendations regarding future research:

Recommendation: Researchers studying opioid prescribing for acute pain should assess how nonopioid interventions (pharmacologic or nonpharmacologic, or both) affect the need for opioids for acute pain as well as assessing their effects on the intermediate outcomes and health outcomes of opioid prescribing strategies.

Recommendation: Researchers studying opioid prescribing for acute pain should address the evidence gaps in the following key priority areas:

- **outcomes of opioid prescribing strategies in key patient populations;**
- **the impact of clinical setting on opioid prescribing strategies; and**
- **the links between intermediate outcomes, such as the number of unused pills or long-term opioid use, and health outcomes, such as pain, mortality, overdose, opioid use disorder, and function.**

1

Introduction

Acute pain can limit an individual's physical activities and participation in family, work, and social roles. Acute pain can be self-managed as recovery occurs. However, some acute pain caused by a medical condition or injury can require medical interventions, including nonpharmacologic and pharmacologic treatments for pain as well as treatments aimed at the underlying cause of pain.

Opioids have long been prescribed to relieve acute pain; morphine and opium have been used for centuries (Collier, 2018). In the United States, opioid prescribing increased steadily from 1999 to 2010 but has decreased since 2012 (Guy et al., 2017). Even with that decrease, however, the amount of opioids in morphine milligram equivalents (MMEs[1]) prescribed per person in 2017 was still around 3 times higher than it was in 1999.

Opioid prescribing in the United States is much higher than in other countries. In 2015, nearly 4 times as many opioids were prescribed in the United States than in Europe (Guy et al., 2017). In 2010, the United States consumed approximately 80% of world's opioid supply despite constituting less than 5% of the world's population (Duthey and Scholten, 2014; Rose, 2018). Opioid prescribing in the United States is higher for some medical specialties and for acute as well as chronic pain. For example, dentists in the United States prescribed opioids 37[2] times more frequently than did dentists in the United Kingdom (35.4 prescriptions/1,000 U.S. population versus 0.5 prescriptions/1,000 UK population) (Suda et al., 2019). For pain management after low-risk surgical procedures (e.g., laparoscopic cholecystectomy or appendectomy, arthroscopic knee meniscectomy, and breast excision), U.S. patients were prescribed opioids at rates 7 times higher than those in Sweden (76% versus 11%) (Ladha et al., 2019).

Along with the rise in opioid prescribing, the number of deaths from drug and opioid overdoses has also risen since 1999. This has led to what many refer to as the "opioid crisis or epidemic" or "opioid

[1] MMEs are used to standardize reporting of the dose of opioids a person receives across different opioids. For example, 50 MMEs per day is equal to 50 mg of hydrocodone (10 pills of hydrocodone/acetaminophen 5/300) or 33 mg of oxycodone (approximately two 15 mg pills of sustained-release oxycodone). See https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf (accessed September 18, 2019).

[2] This text has been revised since prepublication release.

overdose crisis." Even as the amount of opioids prescribed has decreased over the past several years, the rate of opioid-related deaths has continued unabated. Although the reasons for this are multifactorial, unused opioids from excessive prescriptions serve as the most common initial opioid exposure for individuals who use heroin. The use of heroin and its synthetic derivatives is a major factor in the current rise of opioid-related deaths (Cicero et al., 2014). In 2016, 42,249 people died of opioid overdoses (CDC, 2018a). This equates to about 130 Americans dying every day from opioid overdose (CDC, 2018b). By comparison, an estimated 42,000 people will die of breast cancer in 2019 (ACS, 2018). Between 1999 and 2016 the mortality rate among children and adolescents due to prescriptions and illicit opioid use increased by approximately 268% (Gaither et al., 2018).

Thus, clinicians caring for patients with acute pain have two distinct goals: relieving the patient's pain and minimizing the risks of opioids to the patient and to the public health. The committee recognizes that the treatment of acute pain with opioids is one of many contributing factors to the national opioid epidemic. Over the past several years, the opioid overdose epidemic has received national attention and numerous governmental and private organizations have sought to reduce the number of deaths, overdoses, and addictions related to the use of opioids. The 2017 National Academies of Sciences, Engineering, and Medicine (the National Academies) report *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use* contains a comprehensive review of the legal, regulatory, and policy context of opioid prescriptions for pain. The National Academies report summarizes this situation thus:

> The ongoing opioid crisis lies at the intersection of two substantial public health challenges—reducing the burden of suffering from pain and containing the rising toll of the harms that can result from the use of opioid medications. (NASEM, 2017, p. 1)

OPIOID PRESCRIBING PATTERNS

When one examines opioid prescribing trends in detail, a complex picture emerges. In 2006, health care providers wrote 72.4 opioid prescriptions per 100 persons. This rate increased annually by 3.0% from 2006 to 2010, decreased 1.6% annually from 2010 to 2014, and continued to decrease annually by 8.2% until 2017, reaching a rate of 58.5 prescriptions per 100 persons. The average prescribed dose for adults decreased between 2006 and 2016, from 59.7 daily MMEs to 45.3 MMEs. For high-dose opioids (daily MMEs>90), the annual prescribing rate per 100 persons decreased from 11.5 to 5.0 between 2006 and 2017. On the other hand, the average days of supply per opioid prescription increased from 13.3 to 18.3, although the rate of increase was slowing in recent years (CDC, 2018a,b). A recent study showed that between 2005 and 2015, overall opioid prescribing rates for adolescents and young adults (aged 13–17 years and 18–22 years, respectively) in emergency departments (EDs) was 14.9% and 2.8% in outpatient clinic visits (Hudgins et al., 2019). The highest rates of opioid prescribing in the ED for both age groups were for dental disorders, followed by clavicle fractures (adolescents only), and low back pain (young adults only).

The recent reduction in opioid prescribing has been widespread across different specialties and patient populations. A 2019 study found that among enrollees in a large commercial insurer's database, about 54% fewer enrollees received new opioid prescriptions in December 2017 than in July 2012 (0.75% versus 1.63%) (Zhu et al., 2019). Furthermore, the number of clinicians who wrote new prescriptions fell by about 30%, with reductions occurring across all provider specialties and for all diagnostic codes. Dentists were least likely to write prescriptions for long courses of opioids, and primary care clinicians were most likely (Zhu et al., 2019). Data from pediatric populations also indicate a decrease in opioid prescribing. In a study of 1,795,329 patients with a median age of 10 years who underwent ambulatory

surgery from 2010 to 2017, opioid use was found to have dropped from 75% to 67% (Rizeq et al., 2019). Other studies have also documented a similar pattern of reductions in opioid use in pediatric populations (Gagne et al., 2019).

OPIOID-RELATED MORBIDITY AND MORTALITY

Although opioids can relieve acute pain, their use can also lead to short- and long-term risks to the patient, particularly in the case of initial exposures and larger dosages for opioid-naïve patients. One risk is the development of persistent opioid use in opioid-naïve patients who start opioids for acute pain (Barnett et al., 2017; Bateman et al., 2016; Brummett et al., 2017; Delgado et al., 2018; Deyo et al., 2017; Harbaugh et al., 2018; Meisel et al., 2019; Shah et al., 2017; Sun et al., 2016). According to one study, between 4.5% and 9.9% of opioid-naïve patients who fill a prescription for opioids around the time of common surgical procedures end up filling one or more prescriptions for opioids between 90 and 180 days after surgery (Brummett et al., 2017). Another study found that 12 months after total knee arthroplasty, 1.41% of opioid-naïve patients filled more than 10 opioid prescriptions—or more than a 120-day supply—in the 12 months after surgery, as did 1.18% of patients after open cholecystectomy, but only 0.12% of patients had chronic opioid use after cesarean delivery (Sun et al., 2016).

Prescription quantities are also associated with continued use. Prescriptions with higher quantities, based on the number of opioid pills or greater number of days supplied—resulting in a higher total number of MMEs prescribed—are associated with higher rates of persistent opioid use (Barnett et al., 2017; Delgado et al., 2018; Deyo et al., 2017; Meisel et al., 2019; Shah et al., 2017).

Data suggest that a substantial percentage of patients who receive opioids for acute pain do not use all the prescribed pills, particularly after surgery (Bicket et al., 2017; Kumar et al., 2017; Maughan et al., 2016; Monitto et al., 2017). Studies have shown that after cesarean delivery about 50% to 75% of patients had unused opioids (Bateman et al., 2017; Osmundson et al., 2017). After joint or lumbar spine surgery, of the 71% of patients who had stopped opioids at 1 month 37% had more than 200 MMEs in their possession, and fewer than 10% had securely stored or properly disposed of their leftover opioids (Bicket et al., 2019).

A 2017 study in Michigan of patients undergoing 12 common operations found that the quantity of opioid prescribed was significantly greater than quantity consumed (Howard et al., 2018). For 11 of the 12 procedures, the median opioid consumption was less than half of the quantity prescribed. For the entire study population the median number of leftover oral morphine equivalents was 100 (interquartile range [IQR], 25–150). Furthermore, the quantity of opioid prescribed was associated with higher patient-reported opioid consumption even after controlling for postoperative pain, the surgical procedure, and patient-related factors. On the average, patients consumed 5 more pills for every 10 additional pills prescribed (Howard et al., 2018).

Opioids pose risks not only to the patients for whom they are prescribed, but also to family members and to the community. Unused opioid pills from opioid prescriptions can be diverted to family members and friends (Bicket et al., 2019; Hill et al., 2017; Howard et al., 2019; Thiels et al., 2017). These unused pills, which often are not disposed of properly, may be used by the patient for indications other than those for which they were prescribed (e.g., as a sleep aid), or they may be used by someone other than the patient (Bicket et al., 2017; Jones et al., 2014). Individuals with opioid use disorder commonly report that they started by misusing prescription opioids (Ali et al., 2019; Becker et al., 2008; Cicero et al., 2014; NASEM, 2019). Furthermore, there is an association between the size of a patient's opioid prescription and the likelihood of an opioid overdose among the patient's family members (Khan et al., 2019). This association is present in children and adolescents as well as in adults (Khan et al., 2019). Among individuals who misuse prescription opioids, the most common source of opioids was pills

from family members and friends. Among individuals who use heroin, the majority (66%) previously misused prescription opioids (Cicero et al., 2014). Thus, opioid overprescribing, that is, prescribing more opioids than are necessary to control a patient's acute pain, is a factor contributing to the public health epidemic of opioid overdoses.

STANDARDIZING OPIOID PRESCRIBING PRACTICES

The inappropriate variation in opioid prescribing for surgical and medical conditions and the fact that overprescribing is a factor in the continuing opioid epidemic suggest that some guidelines for acute pain management for these conditions would be beneficial for both prescribers and their patients. One approach to setting such standards would be to establish evidence-based prescribing guidelines for opioids for pain management. Although there is considerable literature and guidance on the use of opioids for treating chronic pain, guidelines on acute pain are a relatively recent development.

To address the overprescribing of opioids for acute pain, numerous organizations, ranging from state and local governments to professional societies, individual health care organizations, and hospital departments, have instituted some form of opioid prescribing guidance. For example, New York City has enacted nine recommendations for opioid prescribing in EDs modeled after the Washington State initiatives for regulating opioid prescribing in the ED (Chu et al., 2012; Juurlink et al., 2013). Similar opioid prescribing guidelines have been promulgated by the American Academy of Emergency Medicine (Cheng et al., 2013). Florida used a more conservative approach and passed a bill in 2018 imposing a 3-day limit on opioid prescriptions, unless strict conditions are met for more liberal prescribing of 7 days. Other guidelines vary from a short list of prescription recommendations for the number and dose of opioids to evidence-based clinical practice guidelines (CPGs) developed by professional societies (e.g., the American College of Occupational and Environmental Medicine) or by federal agencies such as the Centers for Disease Control and Prevention (CDC) (Dowell et al., 2016).

Despite widespread efforts to reduce opioid prescribing over the past 5 years—and resulting modest reductions—opioid prescribing remains highly variable within specific indications (as later chapters discuss in detail), and more work is needed to optimize prescribing guidelines. Opioid prescribing practices vary by geographic region (Paulozzi et al., 2014; Schieber et al., 2019), within and among patient populations (Sinnenberg et al., 2017; Tomaszewski et al., 2018), and by providers (Guy and Zhang, 2018; Volkow et al., 2011). This variation in opioid prescribing, together with a lack of guidelines that have been rigorously developed based on evidence, has led to uncertainty among clinicians and regulators about the efficacy and appropriateness of opioid use.

To address the need for a more consistent approach to the development of CPGs, the U.S. Food and Drug Administration (FDA) asked the National Academies to recommend an evidence-based framework that could be used by professional societies, health care organizations, and local, state, and national agencies to develop CPGs for opioid prescribing for acute pain. Such a framework could inform the development of opioid prescribing guidelines and ensure systematic and standardized methods for evaluating evidence, translating knowledge, and formulating recommendations for practice.

COMMITTEE'S CHARGE

FDA tasked the National Academies with establishing a committee to develop a framework to evaluate existing CPGs for prescribing opioids for acute pain indications, to recommend indications for which new evidence-based guidelines should be developed, and to recommend a future research agenda to assist

specialty organizations in the development and dissemination of evidence-based CPGs for prescribing opioids to treat acute pain indications (see Box 1-1 for the committee's Statement of Task).

COMMITTEE'S APPROACH

To accomplish its task, the National Academies empaneled a committee of 15 experts from a diverse group of medical specialties who have experience in the development and use of CPGs (see Appendix A for the committee biographical sketches). The committee recognized that the audience for its report would include not only FDA and other government agencies at the federal, state, and local level that are engaged in mitigating the opioid overdose epidemic, but also professional societies (i.e., medical

BOX 1-1
Statement of Task

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will develop a framework to evaluate existing clinical practice guidelines for prescribing opioids for acute pain indications, recommend indications for which new evidence-based guidelines should be developed, and recommend a future research agenda to inform and enable specialty organizations to develop and disseminate evidence-based clinical practice guidelines for prescribing opioids to treat acute pain indications.

In developing its report, the committee will:

- Identify existing opioid prescribing guidelines for acute pain indications;
- Identify a list of specific medical procedures and conditions associated with acute pain (i.e., develop a prioritized list not to exceed 50) for which opioids are commonly prescribed and for which evidence-based clinical practice guidelines would thus help inform prescribing practices. This list should be prioritized to identify those first which are deemed to have the greatest potential impact on public health;
- Develop a framework for evaluating the evidence base underpinning clinical practice guidelines for opioid prescribing to create a threshold level of evidence to support guidelines and ensure consistency among guidelines;
- Evaluate existing opioid prescribing guidelines for acute pain using this framework to identify specific indications for which prescribing guidelines are not sufficiently evidence-based; and
- Develop a prioritized research agenda, by specific medical procedure or condition (not to exceed 10 of each surgical procedure or medical condition) for which no opioid prescribing guidelines exist or for which more evidence is required to support existing guidelines, to enable the development and availability of comprehensive evidence-based opioid prescribing guidelines for acute pain.

In developing its evaluation framework, the committee will consider the standards established in the 2011 Institute of Medicine report *Clinical Practice Guidelines We Can Trust*. The committee will produce recommendations for how to generate easily accessible, evidence-based, trustworthy clinical practice guidelines for effectively managing acute pain with opioid drugs for specific medical procedures and conditions that the U.S. Food and Drug Administration could use as a reference in its publicly available materials.

and other health care professional societies, such as nurses, physical therapists, and pharmacists), health care organizations, and health insurers that have developed or may develop CPGs for opioid prescribing. Finally, the committee recognized that individual health care providers, and patients, their caregivers, and their communities all have an interest in optimal opioid prescribing not only to manage patients' acute pain, but also to prevent opioids from causing harm.

The committee held five in-person meetings, three of which included public sessions (see Appendix C for the public session agendas). At the first public session, the committee heard from FDA and CDC representatives. The committee gathered information at two subsequent public sessions that convened national experts who delivered specific content relevant to the committee's tasks and engaged in discussions with the committee. The public session in February 2019 focused on identifying surgical procedures and medical conditions associated with acute pain for which opioid analgesics are prescribed. The public session in July 2019 focused on prioritizing a research agenda for selected medical and surgical indications for which no CPGs exist or for which more evidence is required to support existing guidelines. Experts presented state-of-the-science content on acute pain conditions and identified specific gaps in research concerning opioid prescribing.

The committee conducted literature searches to identify current opioid prescribing practices and trends, existing opioid prescribing guidance, information on the use of opioids to treat acute pain for the priority medical and surgical indications it identified, and information on the prevalence and incidence of the selected medical and surgical indications. Literature searches focused on the retrieval and evaluation of evidence-based publications in referred journals with an emphasis on randomized controlled trials, clinical trials, and large observational and cohort studies as an evidence base for opioid prescribing. Committee members also examined available evidence-based CPGs, other guidelines, white papers, national and state reports, and other literature that has informed opioid prescribing for acute pain. Unpublished data presented to the committee during public sessions (e.g., information about the experiences of health care institutions examining the impact of opioid prescribing guidelines and practices on patient-, clinical-, and systems-level outcomes) were also considered by the committee in its deliberations.

Review of the Literature

The committee began developing its list of possible indications by conducting literature searches to identify the most prevalent surgical procedures and medical conditions associated with acute pain or opioid prescribing (see Appendix B). Literature searches were conducted for both adult and pediatric populations. Many of the studies focused on single or selected groups of procedures and were primarily in inpatient settings.

On the basis of the few studies identified from the literature searches, the committee created a preliminary list of approximately 50 surgical and medical indications. For surgical procedures, the committee reviewed peer-reviewed publications on the frequency of surgical procedures performed in the United States. Studies that used large national databases such as those developed for the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project 2014 National Inpatient Sample, the nationwide ambulatory surgery analytic file created from the State Ambulatory Surgery and Services Databases (e.g., Steiner et al., 2017, for surgical procedures), and the research database InVision for Data Mart, a product of OptumInsight Life Sciences, were used as primary data sources by the committee.

For medical conditions, the committee also requested data analyses from CDC. The CDC National Center for Health Statistics, using data collected from the 2016 National Hospital Ambulatory Medical

Care Survey (NHAMCS), provided the committee with the estimated number and percentage distribution of hospital ED visits at which opioids were prescribed at discharge, categorized by diagnosis group. NHAMCS collects annual data on ambulatory care services in hospital EDs and outpatient departments and ambulatory surgery locations based on a national sample of visits to those departments in approximately 500 noninstitutional general and short-stay hospitals (CDC, 2019). The committee was also provided with a list of medical conditions for which opioids are prescribed most frequently in primary care, based on administrative data from a large national health insurer (Brian Bateman, Brigham and Women's Hospital, personal communication, September 3, 2019). This provided the committee with a list of medical indications to consider for prioritization.

The committee also sought the advice of key experts and stakeholders with knowledge of pain management in geriatric, pediatric, and underserved populations; general and specialty surgeries such as dental, obstetric, and orthopedic surgery; emergency medicine; sports medicine; internal medicine; and family medicine. These experts were asked to provide their priority indications for CPG development and the reasons for their selections at the committee's second public session. Committee members also added priority indications to the list based on their own expertise. These sources resulted in a preliminary list of more than 100 surgical and medical indications for which acute pain was considered to be common and for which opioids might be prescribed. The list was then refined to fewer than 50 surgical and medical indications on the basis of the criteria described in Chapter 5, Box 5-1. Further literature searches using PubMed were then conducted for each individual indication to identify studies in adult and pediatric patients that described opioid prescribing practices for that indication. Some studies identified in the peer-reviewed literature reported that a substantial proportion of prescribed opioids were unused following care, and others indicated that some patients requested refills or otherwise sought additional pain relief after receiving an initial opioid prescription. The committee considered that such studies indicated a lack of optimal opioid prescribing and that CPGs could enhance care. The committee sought to identify not more than five studies for each indication that reported on opioid use in a specified U.S. adult or pediatric population, described the methods used to assess opioid use, and detailed opioid prescribing outcomes, such as number of pills remaining after a certain time, number of refills requested, and patient satisfaction with pain control. The existence of such studies was considered in refining the priority list of indications. Further details of how the committee developed its priority list of indications are described in Chapter 5.

ORGANIZATION OF THE REPORT

Chapter 2 of this report focuses on a conceptual model of opioid prescribing for acute pain management. The committee lays out the definition of and background concerning acute pain and examines many of the patient factors that affect acute pain presentation and treatment response, such as age and genetics. Attention is focused on access to acute pain management and the impact of the social determinants of health and other factors on a patient's pain management. In Chapter 3 the committee examines the current state of CPGs, including limitations, common use, and existing guidance on their development as well as examples of organizations, both government and private, that are producing guidelines on opioid prescribing. The committee presents and explains two frameworks for developing evidence-based CPGs in Chapter 4, an analytical framework and an evidence-based framework. It also assesses factors that affect the implementation of CPGs at the provider, organization, and patient levels. Chapter 5 lists the priority surgical and medical indications that the committee identified for which opioids are prescribed and for which evidence-based CPGs would help inform the prescribing practices of health care providers. This chapter also responds to the committee's task to identify existing opioid prescribing guidelines

for acute pain indications. The focus of Chapter 6 is the application of the frameworks developed in Chapter 4 to seven selected surgical and medical indications from the lists in Chapter 5. This chapter shows how the frameworks can be used to identify gaps in the literature and indicates what types of studies are necessary to fill those gaps. These gaps can be used to inform an agenda for future research efforts. Finally, in Chapter 7, the committee summarizes its recommendations for developing or improving evidence-based CPGs for prescribing opioids for acute pain, including which research needs should be emphasized. Appendix A presents short biographical sketches of the committee members, Appendix B provides the committee's literature search strategies, and Appendix C contains the agendas for the committee's public sessions.

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2

Managing Acute Pain

Everyone experiences pain at some point in their lives. Pain can be mild and require no treatment or be treated easily with over-the-counter medications or nonpharmacologic approaches. Both mild and more severe pain may be acute and amenable to treatment, or the pain may be chronic and debilitating. Both acute and chronic pain may be intermittent or recurring, and acute pain may even occur on top of chronic pain resulting from a medical condition (IOM, 2011). People with acute pain need adequate pain relief, and many cases of mild acute pain do not require treatment with medications; while for more severe pain, analgesics other than opioids may be effective, so opioids are not needed. However, for severe acute pain or for acute pain that does not respond to other treatment options, opioids can often provide effective relief, and thus are sometimes needed. On the other hand, it is also important to take into account the risks of opioid prescribing to patients and to public health, including chronic opioid use, opioid use disorder, and the availability of unused pills for diversion to those for whom they were not prescribed. Finding a balance between the management of acute pain and the risks of opioid prescribing is a challenging task.

Opioids have long been prescribed to relieve acute pain. Although the widespread use of opioids[1] for pain management began in the 1990s, some opioids such as morphine and opium have been used for centuries (Collier, 2018). In part, the increased use of opioids was the result of efforts in the late 1990s and early 2000s to reduce acute, chronic noncancer, and cancer pain. In 2000, The Joint Commission (2016) issued standards for pain assessment and management practices that imposed criteria for health care organization policies addressing pain that increased the use of patients' self-reported pain to guide pain management. By 2009, in response to detrimental reports of overly aggressive treatment of pain, the standard that all patients be assessed for pain was revised to require this standard in only behavioral health care (Baker, 2017).

[1] "Traditionally, the term opiates refers to substances derived from opium, such as morphine and heroin, while opioids refers to synthetic and semisynthetic opiates. However, the term opioids is now often used for the entire family of opiates, including natural, semisynthetic, and synthetic" (NASEM, 2017a, p. 23).

Overall, pain may cause physical and emotional distress and compromise a person's ability to meet family, job, school, and other responsibilities. Acute pain also harms a person's quality of life, including affecting sleep, physical functioning, and mental health (Sinatra, 2010). Furthermore, suboptimal pain management can contribute to increased morbidity, slow recovery, prolonged opioid use during and after hospitalization, an increased cost of care, and an increased risk of progression to chronic pain (Gan, 2017). Neonates and very young infants may be more vulnerable to the long-term effects of repeated pain on neurodevelopment and neuroendocrine and immune response (Hadjistavropoulos et al., 1997). For health care providers, alleviating pain is a primary responsibility. The Institute of Medicine[2] (IOM) report *Relieving Pain in America* declared as its first guiding principle, "Effective pain management is a moral imperative, a professional responsibility, and the duty of people in the healing professions" (IOM, 2011, p. 3).

This chapter describes the clinical context of acute pain, including the presentation of acute pain, and the pathways by which patients seek and receive treatment for acute pain.

DEFINITIONS

Many terms are used to describe the possible adverse effects that may result from opioid use to treat acute pain, including the term "acute pain" itself. These terms are discussed briefly below.

Acute Versus Chronic Pain

The committee considered having a definition of "acute pain" to be an integral part of its task. The definition it settled on for acute pain was derived from multiple authoritative sources, some of them contradictory. The Centers for Disease Control and Prevention (CDC) emphasizes the contrasting time-dependent differences between acute and chronic pain, with acute pain often described in terms of not being chronic.

The National Pain Strategy uses physiologic, behavioral, and time-dependent criteria to define acute pain as "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" (HHS, 2016, p. 11). This definition is also used in the pain taxonomy classification of acute pain conditions developed by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks; the American Pain Society; and the American Academy of Pain Medicine, with a further explanation that such pain typically lasts up to 7 days but can be prolonged to 30 days (Kent et al., 2017). The 2011 IOM report *Relieving Pain in America* also defined acute pain as being of sudden onset and of short duration, emphasizing that acute pain is usually linked to a specific event, injury, or illness. It may also be recurrent with pain-free periods. The committee recognizes that acute and chronic pain are on a continuum and that acute pain may transition to chronic pain over time.

The 2016 guidelines for the management of postoperative pain—developed and endorsed by several professional pain societies—reference persistent acute pain but without a specific timeframe (Chou et al., 2016). Based on the integration and interpretation of existing definitions of acute pain (Chou et al., 2016), the committee considers acute pain for the purposes of this report to include a sudden onset of

[2] As of March 2016, the Health and Medicine division of the National Academies of Sciences, Engineering, and Medicine continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM). The IOM name is used to refer to publications issued prior to July 2015.

pain that lasts no longer than 90 days. Pain that lasts longer than 30 days but less than 90 days is often referred to as subacute pain and represents a transition between acute and chronic pain.

As noted in the 2017 National Academies of Sciences, Engineering, and Medicine (the National Academies) report *Pain Management and the Opioid Epidemic*, opioids have long been prescribed for the effective management of acute pain, such as postoperative and postprocedural pain, "and they have been found to be more effective than placebo for nociceptive and neuropathic pain of less than 16 weeks' duration" (Furlan et al., 2011; NASEM, 2017, p. 53). However, for some types of acute pain, such as low back pain and pain after third molar extractions, the efficacy of opioids is less clear and their superiority to other medications is not established (Deyo et al., 2015; Friedman et al., 2015; NASEM, 2017). The 2017 National Academies report also stated that:

> Pain diagnosis currently depends on clinical examination and testing (laboratory, imaging) to identify the etiology of the pain. The pain condition is described in terms of the pain's location (e.g., orofacial pain, temporomandibular joint disorder, migraine, low back pain) and/or type (somatic pain is caused by injury to skin, muscles, bone, joints, or connective tissues and is nociceptive; visceral pain arises from the internal organs and is nociceptive; and neuropathic pain is presumed to be caused by a demonstrable lesion or disease of the peripheral or central somatosensory nervous system). Duration of pain is commonly defined as acute (less than 6 weeks), subacute (6–12 weeks), or chronic (more than 12 weeks). (pp. 147–148)

Chronic pain is frequently considered to be pain that lasts longer than 3 months or past the time of normal tissue healing (Dowell et al., 2016a). An extensive discussion of the causes of and treatments for chronic pain may be found in the 2011 IOM report *Relieving Pain in America*. Chronic pain may cause changes in the peripheral and central nervous systems such that it can become a disease in its own right. Furthermore, chronic pain has significant physiological (e.g., changes in brain anatomy), psychological (e.g., depression and anger), and cognitive effects (e.g., pain catastrophizing) that may worsen over time. Causes of chronic pain include an underlying disease or medical condition, an injury, medical treatment, inflammation, neuropathic pain, and unknown causes (IOM, 2011).

Notably, recent studies have shown that chronic opioid use may occur following surgery (Brummett et al., 2017). Bateman et al. (2016) found that approximately 1 in 300 opioid-naïve women become persistent prescription opioid users following cesarean delivery. Sun et al. (2016) found that male sex, age older than 50 years, and a preoperative history of drug abuse, alcohol abuse, depression, benzodiazepine use, or antidepressant use were all associated with chronic opioid use among adult surgical patients. Risk factors for persistent opioid use among pediatric surgical patients include older age, female sex, previous substance use disorder, and preoperative opioid use (Harbaugh and Gadepelli, 2019). Numerous studies have found also that postoperative opioid use may be correlated with patient factors beyond patient-reported pain or procedure type—such as anxiety, mental health conditions, medical comorbidities, and prolonged opioid use—that may not entirely reflect the severity of ongoing pain (Badreldin et al., 2018; Brummett et al., 2013; Committee on Practice, 2018; Hilliard et al., 2018; Kelly et al., 2018; Velanovich, 2000). For example, Hah et al. (2017) found that chronic opioid use after surgery was associated with presurgical opioid use, lower socioeconimic status, preoperative pain, and the use of antidepressants.

Opioid Use

The committee adopted the following definitions related to opioid use for this report (see Box 2-1). Unless otherwise noted, the definitions are from the report *Pain Management and the Opioid Epidemic* (NASEM, 2017).

BOX 2-1
Key Definitions

Diversion is the transfer of regulated prescription drugs from legal to illegal markets; as used in this report, it does not refer to the sharing of drugs with friends, family members, or other contacts for medical or nonmedical purposes.

Misuse is any use of a prescription medication beyond what is directed in a prescription, including (1) medically motivated use more frequently or in a higher dose than prescribed, (2) nonmedically motivated use by the person to whom the drug has been prescribed, (3) medical use by a person other than the person to whom the drug has been prescribed, and (4) nonmedical use by a person other than the person to whom the drug has been prescribed. Misuse also includes sharing of drugs.

Opioid use disorder is defined in the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (DSM-5) as the problematic pattern of opioid use leading to clinically significant impairment or distress (APA, 2013). See the DSM-5 for the specific diagnostic criteria.

Opioids relieve acute severe pain via the μ–opioid receptor in the nervous system. Opioids used for acute pain typically vary with regard to half-life and duration of action, for example, some opioids with a short half-life have a long duration of action because they have a sustained-release formulation. One advantage of using opioids to treat pain is that they come in a variety of formulations including oral, intravenous, transdermal, intranasal, epidural, and intrathecal. However, in spite of variation in the potency of various opioids (as morphine milligram equivalents [MMEs]), there is little evidence to suggest that "one opioid analgesic is superior to another in its ability to manage either acute or chronic pain" (p. 54), or that more potent opioids are associated with higher rates of adverse effects (Murphy et al., 2018).

In the primary care setting, back, neck, and joint pain; musculoskeletal injury; and headache are among the most common patient complaints (Mundkur et al., 2019), and opioids are frequently prescribed for them (Brian Bateman, Brigham and Women's Hospital, personal communication, September 6, 2019). For example, one investigation using records from a large health insurer found that among 230,958 patients in initial pain encounters in a primary care setting for which an opioid prescription was written, the top three pain complaints were joint pain (71,735 encounters), back pain without radiculopathy (54,682 encounters), and headache (40,005 encounters) (Mundkur et al., 2018). Pain is also a common complaint in emergency departments (EDs). From 2000 to 2010, approximately 45% of ED visits were associated with a primary symptom or diagnosis of pain (Chang et al., 2014), and data from the 2016 National Hospital Ambulatory Medical Care Survey (NHAMCS) showed that in more than 20% of ED visits, the principal reason for the visit was some form of pain (the most common reason was abdominal pain at 8.6%) (Rui et al., 2016). The pain-related discharge diagnoses most likely to be associated with an opioid prescription were nephrolithiasis (62.1%), neck pain (51.6%), and dental/jaw pain (49.7%) (Kea et al., 2016).

An analysis of data from the NHAMCS and the National Ambulatory Medical Care Survey for Adolescents and Young Adults showed that opioid prescribing rates were highest for adolescents and young adults presenting to the ED with dental disorders, followed by clavicle and ankle fractures (Hudgins et al., 2019). Among patients who undergo inpatient or outpatient surgery, more than 80%

report pain at discharge, and of these patients about 75–86% reported their pain as severe or extreme (Apfelbaum et al., 2003; Gan, 2017; Gan et al., 2014; IOM, 2011). Data show that medical opioid use among opioid-naïve high school seniors is independently associated with a 33% increase in risk of future opioid misuse after high school (Miech et al., 2015). Adolescents who take opioids, whether prescription or illicit, may be particularly vulnerable to subsequent misuse and substance use disorder (Cerda et al., 2015; Kelley-Quon et al., 2019; Miech et al., 2015). As a result of the increase in opioid misuse and deaths in the United States, a number of professional societies, government agencies, state legislatures, health care organizations, and health insurers have taken a variety of steps to reduce the number of opioid prescriptions, pills prescribed, and total dispensed MMEs (Davis et al., 2019; Dowell et al., 2016b; Schuchat et al., 2017).

PRESENTATION AND TREATMENT OF ACUTE PAIN

There are many effective treatments for acute pain. The 2011 IOM report *Relieving Pain in America* found that "Pain care must be tailored to each person's experience" (p. 8) because people vary in their pain tolerance and in their need for pain management. Appropriate and timely treatment of the underlying cause of pain is often a crucial aspect of pain relief. For example, pain management for an ankle sprain or fracture may include immobilization, rest, ice, compression, and elevation of the damaged area, whereas for a back sprain, bed rest and heat may offer effective pain relief. CDC recommends a stepwise approach to treating pain, using nonopioid modalities first and as adjuncts before using opioids (Dowell et al., 2016a; WHO, 1990). The 2017 National Academies report *Pain Management and the Opioid Epidemic* stated:

> there are some circumstances in which nonopioid analgesics (e.g., nonsteroidal anti-inflammatory drugs) are likely to be as effective as opioids, or more so, for reducing pain associated with the conditions for which they are indicated, and when used appropriately, these analgesics carry a lower risk of adverse outcomes relative to opioids. (p. 4)

Interventional, regional anesthetic approaches are also effective for some indications (e.g., nerve blockades for total knee replacement). Nonpharmacologic interventions, such as acupuncture, physical therapy, exercise, cognitive-behavioral therapy, and mindfulness meditation may also be effective for pain control (NASEM, 2017).

The committee recognizes that there are major injuries, diseases, operations, and treatments with known severe pain and that patients with these indications may require immediate access to opioids. For example, patients with severe sickle cell vaso-occlusive crisis should not be subjected to first-line treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or other nonopioids when they present with severe pain. Patients recovering from an extensive scoliosis spine fusion should also have immediate access to opioids because of the severity of their pain. However, medical innovations may change a clinician's approach to the management of a patient's acute pain. For example, the use of regional anesthetic techniques such as liposomal bupivacaine or collagen mesh-embedded bupivacaine may supplant the need for opioids as these analgesic treatments become more widely used. And the use of indwelling catheters for specific nerve blocks, especially for orthopedic procedures, may obviate the need for opioids for postoperative pain.

A patient's pain presentation may also be influenced by ethnic, racial, physiological, cultural, and religious factors (Green et al., 2004; Meints et al., 2019; Mossey, 2011). Some people from racial and ethnic groups, such as African Americans, Hispanics, and Native Americans, report a higher prevalence

of pain symptoms for certain medical indications than the white population (Campbell and Edwards, 2012). Given the patient-specific factors that can influence pain management, it follows that special considerations may influence the approach clinicians take when prescribing opioids. These factors include

- patients who have not had appropriate pain treatment;
- patients who are unable to communicate their pain, such as infants or those with cognitive impairments;
- patients with chronic pain who are already using opioids and might be opioid-tolerant;
- patients in whom the pharmacology of opioids may differ from the typical, such as children or the elderly;
- patients for whom the understanding of or adherence to a treatment plan of care may be challenging;
- patients who may be at risk for substance use disorder; and
- patients who have genomic or other medical factors that may affect their response to opioid treatment.

Optimal postoperative pain management requires an understanding of each patient-specific factor. In the sections below, the committee considers patient, population, and clinician factors that influence both the presentation and the treatment of acute pain (see Figure 2-1). All of the factors in the boxes may influence a clinician's decision to prescribe opioids for a patient's acute pain. Health care settings and access to care are discussed in later sections.

Age

The presentation of acute pain may vary by age, with, for example, such groups as the elderly, infants, and neonates presenting differently from typical adults (Bartley and Fillingim, 2013; Campbell and Edwards, 2012; Edwards et al., 2001; Fillingim et al., 2009; Green et al., 2003; Pieretti et al., 2016). Furthermore, several studies have found that a person's pain threshold may change as he or she ages (Kaye et al., 2010). Acute postoperative pain may be intensified by certain factors, such as fear, anxiety, coping style, and by a lack of social support in both children (Verghese and Hannallah, 2010) and adults (Kennedy et al., 2019).

Infants and young children rely on caregivers to assess their pain intensity, and such pain assessments often involve behavioral and physiological parameters, since self-reported measures may not be possible in preverbal children or accurate in hospitalized young children (Berde and Greco, 2011). Similarly, some older adult patients who experience acute pain may be unable to clearly communicate their symptoms because of aging-related cognitive issues, including advanced dementia (Morrison and Siu, 2000; Schuler et al., 2004). Elderly patients, especially those with dementia, and young children are also more likely to have their pain undertreated (Birnie et al., 2014; Krauss et al., 2016; McAuliffe et al., 2012).

There are several changes in pharmacokinetics and pharmacodynamics that occur with age. Smith (2009) found that reduced clearance of morphine, codeine, fentanyl, and oxymorphone in older patients suggested that these patients begin with lower initial doses. Pain management must also account for patients in whom the pharmacodynamics of an opioid are different, such as children, the elderly, pregnant or nursing women, and burn or trauma patients (Finley et al., 2014; Keene et al., 2011; Malcolm, 2015; Raymond et al., 2018).

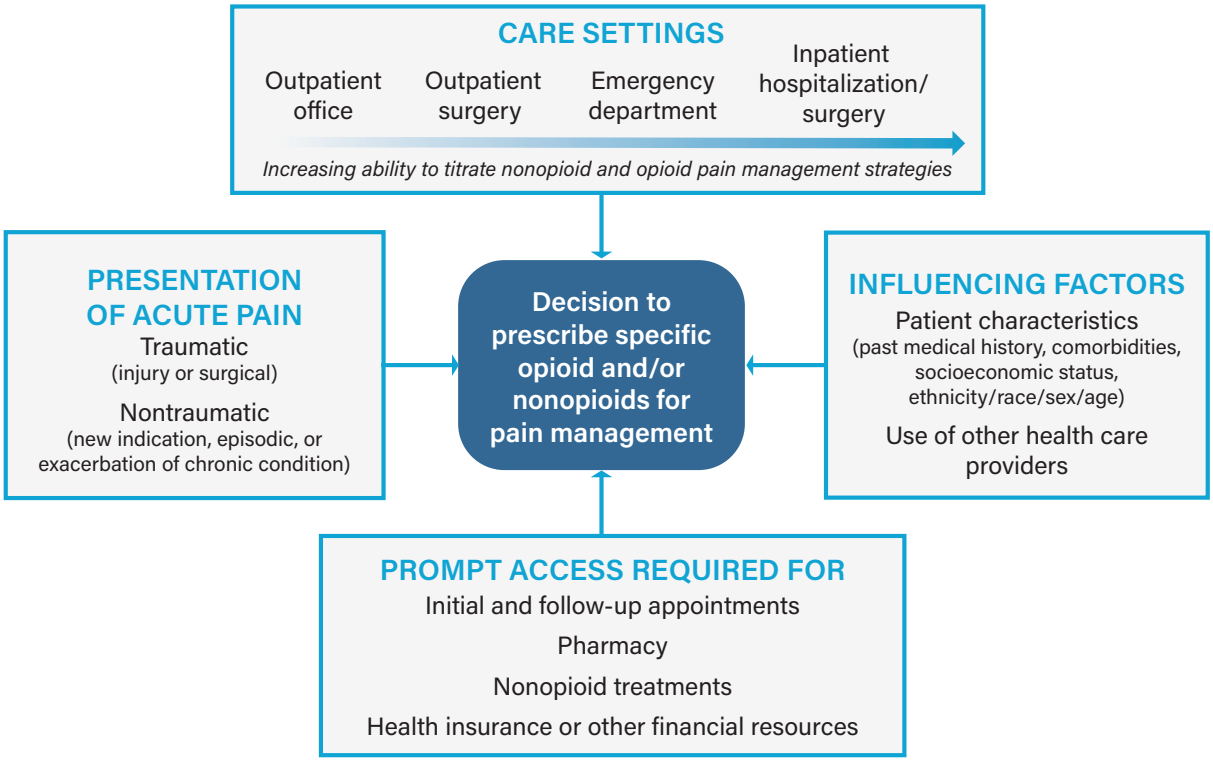

FIGURE 2-1 Clinical factors that influence the decision to prescribe opioids for a patient with acute pain.

Sex

Some research suggests sex differences may also exist in the processing of pain; these differences can inform clinical pain management (Paller et al., 2009). However, results are mixed. While some studies show that women may demonstrate higher levels of pain sensitivity and have greater prevalence of many commonly observed clinical pain signs and symptoms than men, which appears to be due in part to differences in genetics, sex hormones, and attitudes to pain (Bartley and Fillingim, 2013; Fillingim, 2018; Fillingim et al., 2009; Otto et al., 2019; Pieretti et al., 2016), others show little difference in pain perception between the sexes (Gadkaree et al., 2019). Cattaneo et al. (2017) found that following major abdominal surgery, there was a statistically significant daily periodicity ($p<0.001$) in morphine consumption with consumption higher around 2 AM (rate 0.4 mg/min) and lower around 12 PM (rate 0.05 mg/min). The daily periodicity of morphine consumption was different between men and women ($p=0.004$), with males consuming more morphine during the night; there were no differences in daily periodicity for the categories of age and body mass index. Romano et al. (2019) also found that among men and women (median age 73) with worsening cognition, women reported significantly less unpleasantness with the percept of moderate pain and men reported significantly higher unpleasantness with moderate pain perception ($p=0.033$).

Body Weight

Body weight, which is related in part to sex, age, and other factors such as comorbidities, as well as the growing problem of obesity in the U.S. population, may also affect opioid prescribing requirements

and the presentation of adverse effects. Most research on the use of opioids in obese individuals has focused on administration during anesthesia and in the immediate postsurgical period (Lloret-Linares et al., 2013; Schug and Raymann, 2011), rather than prescribing at discharge. Patanwala et al. (2014) found that body mass index did not affect a patient's pain response to a fixed dose of intravenous morphine administered in the ED. Similar results were found by Xia et al. (2014) for intravenous hydromorphone administered to patients with body weights ranging from 45 to 157 kg. The authors of both studies suggest that there is no advantage to weight-based opioid dosing versus fixed opioid dosing for pain response. As such, weight-based dosing is not typically considered in adult opioid dosing; however, extremes in weight should be considered as they may increase the risk for adverse effects, including respiratory depression in patients who are obese (Lloret Linares et al., 2009). Moreover, multiple factors including unique pharmacokinetics, developmental characteristics, and extreme variations in weight (0.4–150 kgs) require weight-based dosing in neonates, infants, and children (Kopecky, 2019).

Drug Interactions

Opioids are often taken concurrently with other pharmaceuticals—prescribed, over-the-counter, and illicit—and this use can result in drug interactions. Between 2016 and 2017, an estimated 267,000 ED visits were associated with prescription opioid harms (Lovegrove et al., 2019). Data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project showed that almost half of the visits (47.6%) were associated with nonmedical opioid use, 38.9% with therapeutic use, and 13.5% with self-harm. Use of other pharmaceuticals, particularly benzodiazepines, were co-implicated in ED visits across all three groups. Concurrent use of illicit drugs, particularly marijuana, was most common among nontherapeutic visits, whereas alcohol was the most commonly associated with opioids taken for self-harm.

Drug interactions fall into two broad categories: pharmacodynamic and pharmacokinetic. In pharmacodynamic interactions, drugs directly influence the effect of each other (Cascorbi, 2012), as is the case with opioids and benzodiazepines. Both drugs are sedatives and suppress breathing. In 2016, it was estimated that as many as 30 million people in the United States may have used benzodiazepines, although misuse appears to be relatively uncommon (only 2.1% reported misuse) (NIDA, 2018). The National Institute on Drug Abuse (NIDA) reports that more than 30% of overdoses involving opioids also involve benzodiazepines (NIDA, 2018). Indeed, the combination of opioids and benzodiazepines has been shown to significantly increase the risk for overdose (odds ratio [OR]=5.05, 95% confidence interval [CI] 3.68–6.93) during the first 90 days of co-prescribing in patients older than 65 years of age; however, the risk decreased to 1.87 (95% CI 1.25–2.80) at 91 to 180 days of concurrent use (Hernandez et al., 2018). Other important pharmacodynamic interactions may occur between opioids and other central nervous system (CNS) depressants such as muscle relaxants, barbiturates, anxiolytics, benzodiazepine-like and nonbenzodiazepine hypnotics and sedatives (e.g., Zolpidem), gabapentinoids, antihistamines, antipsychotics, and alcohol (Dowell et al., 2016). The Centers for Medicare & Medicaid Services has issued a memo warning Medicare sponsors about those drugs because when used in conjunction with opioids they can potentiate the effect of the latter drugs (Majestic, 2018).

In pharmacokinetic drug interactions, one medication impacts the absorption, distribution, metabolism, or elimination of another medication (Cascorbi, 2012). Pharmacokinetic enhancers for opioids are strong inhibitors of the cytochrome P450 enzymes, specifically CYP3A4. Inhibition of CYP3A4 leads to a subsequent increase in the serum concentration of the opioid due to its decreased metabolism. Examples of cytochrome P450 enzyme inhibitors are drugs for the human immunodeficiency virus, antifungals, and some antibiotics (Majestic, 2018). Opioids metabolized by the cytochrome P450

system (e.g., codeine, oxycodone, hydrocodone, fentanyl, tramadol, and methadone) are associated with numerous drug–drug interactions that can result in either a reduction in opioid effect or excess opioid effects. Conversely, opioids that are not metabolized by that system (e.g., morphine, oxymorphone, and hydromorphone) tend to be involved in fewer CYP450-associated pharmacokinetic drug–drug interactions (Overholser and Foster, 2011). Some opioids (e.g., tramadol, codeine) can be considered pro-drugs in that their metabolism results in compounds with greater activity; if this metabolic activity is inhibited, a decreased analgesic effect would be expected. Conversely, when the administered opioid is active and metabolized to inactive metabolites (e.g., fentanyl), inhibition interactions are expected to prolong or enhance opioid effects (Overholser and Foster, 2011). However, the issue may be further complicated in that some opioids are metabolized to both inactive and active metabolites by multiple enzymes. An example of this is oxycodone, for which the enzyme CYP3A converts oxycodone to the less active compound noroxycodone and the enzyme CYP2D6 converts oxycodone to the more active compound oxymorphone.

Drug–drug interactions may also influence whether clinicians should prescribe opioids to patients. For example, taking opioids with benzodiazepines, alcohol, or medications that depress the CNS have resulted in serious side effects such as difficulty breathing and even death (Hwang et al., 2016; Jones et al., 2014; Park et al., 2015). Even tobacco use may affect opioid use. Radcliff et al. (2017) found that ED patients with active tobacco use had a poorer response to the administration of intravenous opioids for severe pain than did patients with inactive tobacco history. U.S. Food and Drug Administration (FDA)-approved drug labels for opioids formulations contain "black box" warnings that specifically call out the risks and mitigation strategies for drug interactions between opioids and other common drugs such as benzodiazepines, other CNS depressants, and alcohol. Interactions with other drugs such as monoamine oxidase inhibitors may also be indicated (NLM, n.d.).

Comorbidities

When considering the appropriate treatment modality for a patient with acute pain, organ function and other medical comorbidities need to be evaluated. Comorbidities may be the result of aging (e.g., osteoarthritis), injury, or have other known or unknown causes (e.g., cardiovascular disease, diabetes, cancer).

Opioid metabolism and excretion can be impaired by liver and kidney disease, and special consideration needs to be taken in the choice of analgesia treatment for patients with these conditions (Davison, 2019; Soleimanpour et al., 2016). The use of opioids to treat acute pain in the elderly or people with kidney disease may be complicated by the fact that the use of alternative analgesics such as NSAIDs are contraindicated for those populations (Horl, 2010).

As the use of prescription opioids has increased in recent years, so too has the number of individuals receiving medications for substance use disorder and addiction treatment with methadone or buprenorphine (Huxtable et al., 2011). Both factors have, in turn, increased the number of opioid-tolerant patients, making the treatment of acute and chronic pain more difficult. Studies have demonstrated that past opioid use or dependence is likely to result in increased mortality, postoperative complications, and longer hospital stays (Best et al., 2015; Cooney and Broglio, 2017). As a benchmark, FDA defines opioid-tolerant individuals as having received the equivalent of at least 60 mg/day of oral morphine, 25 mcg/hour of transdermal fentanyl, 30 mg/day oral oxycodone, 8 mg/day of oral hydromorphone, 25 mg/day of oral oxymorphone, or an equivalent analgesic dose of another opioid for at least 1 or more weeks (FDA, 2016).

Risk factors for developing substance use disorder include, but are not limited to, being a young adult (aged 18–34 years), being male, having a history of psychiatric outpatient visits or psychiatric

diagnosis, and having been diagnosed with nonopioid substance use disorder, depression, posttraumatic stress disorder, or hepatitis (Edlund et al., 2010; White et al., 2009).

For adolescents, environmental factors such as family life and peer relationships as well as major life events are important factors to consider when prescribing opioids (Swadi, 1999; Thatcher and Clark, 2008; Whitesell et al., 2013; Zimmerman and Farrell, 2017). Adolescents and adults who experienced adverse childhood events may be at increased risk for substance misuse (Hailes et al., 2019; Quinn et al., 2019). Other risk factors for opioid misuse include a history of medical use of a prescription opioid (Miech et al., 2015) and psychosocial factors such as depressive episodes (Edlund et al., 2015) and anxiety (Boyd et al., 2014).

Genetics

Certain risk factors for opioid use disorder have been traced to genetics, and early research suggests it may be possible to identify this risk by examining an individual's genotype (Koolen and Van der Rijt, 2017). Certain genetic variants in sensitivity to pain and to the rewarding properties of opioids, along with differences in how people metabolize opioids, will likely affect their response to treatment. Genetic factors can also interact with psychosocial factors such as stress and pain catastrophizing to influence pain (Fillingim, 2019).

In the future, genetic screening may enable clinicians to tailor opioid doses for acute pain for individual patients (Berrettini, 2017; Madadi et al., 2013). Also, differences in opioid metabolism due to variations in metabolic phenotypes have been demonstrated in children. In particular, postoperative deaths were reported among children who were prescribed codeine, with the deaths attributed to atypical cytochrome CYP2D6 pharmacogenetics (Kelly et al., 2012). Children who have CYP2D6 ultra-rapid metabolizer genotypes are at increased risk for serious adverse effects due to the excessive conversion of codeine into morphine, whereas in children who have significantly reduced levels of this enzyme, codeine has poor efficacy. Safety concerns regarding the use of codeine in children led FDA to restrict its use for this population (FDA, 2018). Balyan et al. (2017) examined plasma levels of oxycodone and oxymorphone in 30 children who were administered oral oxycodone postoperatively. Children with an extensive metabolizer phenotype were found to have a higher conversion of oxycodone to oxymorphone than children who were poor or intermediate metabolizers. Similar studies conducted among adults using a randomized controlled trial design suggest the risk of overdose or death from opioid treatment can be decreased through an understanding of a patient's CPY2D6 phenotype (Linares et al., 2014).

Health Disparities

Ideally, patients who have similar presentations of acute pain should be treated in a similar manner, but this is not always the case and can result in health disparities. Health disparities can result from a number of factors such as socioeconomic differences, ethnicity and race, treatment setting, access to care, and implicit or explicit clinician bias.

Staton et al. (2007) found that physicians in primary care centers were twice as likely to underestimate pain in black patients as in all other ethnicities combined. A meta-analysis of 14 studies published from 1990 to 2018 comparing racial and ethnic differences in the administration of analgesia for acute pain in EDs showed that black and Hispanic patients were less likely than white patients to receive analgesia for acute pain (OR=0.60, 95% CI 0.43–0.83 and OR=0.75, 95% CI 0.52–1.09, respectively) (Lee et al., 2019). Using data from the National Ambulatory Medical Care Survey, Ly et al. (2019) found that

among patients presenting with abdominal pain in an outpatient setting, black patients were 6.0% less likely and Hispanic patients 6.3% less likely than white patients to receive opioids; similarly, black and Hispanic patients presenting with back pain were 7.1% and 14.8% less likely, respectively, than white patients to receive opioids for back pain. These disparities may also be seen in children of parents with limited English proficiency. Jimenez et al. (2014) found that among 237 hospitalized children of parents with limited English proficiency there were fewer postsurgical pain assessments and higher levels of recorded pain before they received opioids than among 237 children of parents who were proficient in English.

Institutional and structural racism as well as other forms of discrimination in the United States influence the provision of medical care (IOM, 2003). Populations that have historically been discriminated against in the United States, such as people of color, are more likely to have their pain undertreated than other groups. One review of 34 studies of pain treatment found that blacks experienced opioid prescription disparities for both traumatic/surgical pain and nontraumatic/nonsurgical pain, whereas these disparities were ameliorated for Hispanics with traumatic/surgical but remained for nontraumatic/nonsurgical pain (Meghani et al., 2012). Both Hispanics and blacks experienced opioid treatment disparities with regard to nontraumatic or nonsurgical pain and opioid prescriptions. For blacks, opioid treatment disparities remained consistent across pain types, settings, study quality, and data collection periods. One study found that black pediatric patients with appendicitis were less likely to receive opioid analgesia for moderate and severe pain than white patients (12.2% versus 33.9%) (Goyal et al., 2015). A study by Pletcher et al. (2008) found that between 2001 and 2005, whites were more likely to receive an opioid prescription in the ED (31%) compared with blacks (23%), Hispanics (24%), and Asians (28%, $p<0.001$ for trend). These prescribing differences did not decrease over time and were evident for all types of pain visits, were more pronounced with increasing pain severity, and were detectable for long-bone fracture and nephrolithiasis as well as among children.

Another, later study found that non-Hispanic blacks were less likely than non-Hispanic whites to receive an opioid prescription at discharge from an ED for "non-definitive" conditions such as back pain and abdominal pain (OR=0.56–0.67, p value<0.05), but not for toothache (Singhal et al., 2016). However, there were no significant differences in the prescribing of opioids between the two groups for the definitive diagnoses of long-bone fracture and kidney stone and no significant differences for Hispanics and any diagnosis.

Clinician factors, such as implicit or explicit bias in patient treatment, may contribute to disparities in the management of acute care and are related to differences in pain assessment and treatment. For example, some evidence suggests that clinicians tend to underestimate the pain of patients of color (Anderson et al., 2000). Furthermore, the authors found that patients of color report that clinicians often do not believe they have pain or do not understand their pain. Individuals with mental illness or a substance use disorder have historically been undertreated when experiencing pain. This is primarily due to the clinicians' misperception of patients with substance use disorders—and those with mental illness—as drug-seeking and noncompliant (Haller and Acosta, 2010; Iocolano, 2000).

Clinical uncertainty on the part of clinicians (e.g., in interpreting disease symptoms in minority patients) can itself be a source of disparate treatment (Balsa et al., 2003). Clinician biases, implicit or explicit, about patients of color can also contribute to disparities (IOM, 2003). In a study that examined physician bias, investigators found that stereotypes about various racial groups were likely to influence provider communications about health recommendations (van Ryn, 2002). When cognitive capacity is taxed, memory is biased toward information that is consistent with stereotypes, which then leads to the underestimation and undertreatment of pain (Mathur et al., 2014; Staton et al., 2007; Trawalter et al., 2012).

Health Literacy

Health literacy, that is "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" (HHS, n.d.) and efforts taken to account for differences in health literacy can impact the effective management of acute pain. Pain management plans are most effective when they address pain, account for comorbid conditions, and have the patient's understanding and agreement. Comorbidities, such as schizophrenia and depression or cognitive impairment, may impair an individual's ability to understand and follow a care plan. Health literacy, numeracy, and language barriers may have a similar impact on care plans. For example, a 2018 study found that among patients with musculoskeletal pain who received primary care, 6-month physical function scores were lower and pain intensity scores were higher among those with poorer health literacy; however, a limitation of the study was that health literacy was assessed with only a single-question literacy screen (Lacey et al., 2018). Health literacy correlated with older age, less education, comorbidities, and mental health but not with gender. Thus, clinicians should consider what supportive factors a patient may require to implement the care plan (e.g., the presence of a caregiver or nurse to assist with a treatment regime), should ensure that appropriate follow-up is scheduled, and should determine whether the patient has interim access to care for urgent issues, if needed.

ACCESS TO APPROPRIATE ACUTE PAIN MANAGEMENT

Implementing opioid treatment requires patients to have access to appropriate, timely management of their acute pain. Such access, as noted in Figure 2-1, requires a multistep process involving different aspects of the health care system, which can be affected by the health care setting in which the presentation, diagnosis, and treatment of the acute pain occurs. Appropriate treatment for pain will be possible only if each step in the process is achieved. In this section, the committee considers the factors that affect a patient's clinical evaluation, pain management strategy, and access to those strategies.

Health Care Settings

Patients seek and receive treatment for acute pain in diverse health care settings, including hospitals, EDs, primary care offices, urgent care centers, long-term care facilities, pharmacies, and specialty clinics such as pain management, surgery, pediatrics, internal medicine, chiropractic, obstetrics and gynecology, and osteopathy. The health care setting in which pain is treated, including follow-up care, plays an influential role on the clinician's ability and decision to prescribe an opioid after discharge and how to determine the proper dose. Specifically, there is variability in a clinician's ability to prescribe and titrate nonopioid and opioid pain management strategies during the health care encounter prior to writing a prescription for outpatient pain management. During a 15- to 30-minute general outpatient office visit, a clinician will not typically have the opportunity to test pain management strategies. This might lead to prescribing a default amount of opioids to avoid undertreatment of pain at home once the anesthesia wears off (e.g., after a third molar extraction), which in turn might result in overprescribing.

In contrast, acute pain in the ED can be treated initially with an array of nonopioid and nonpharmacologic alternatives including NSAIDs, acetaminophen, and topical anesthetics. The clinician can then observe the patient's response to these treatments and provide opioids if pain control is insufficient over the course of several hours. Finally, inpatient hospitalization for acute medical pain or after inpatient surgery can provide an extended opportunity to titrate pain control over a period of more than 1 day. Patients who do not require opioids during the final 24 hours of hospitalization often do not require opioid prescriptions at discharge (Hill et al., 2018).

Other setting-specific considerations include the ability to establish follow-up encounters with patients. For example, primary care clinicians may be able to schedule a follow-up visit, telemedicine visit, or phone call to determine the need for a refill, whereas ED clinicians typically do not have ongoing relationships with patients once they are discharged and usually recommended that patients see other providers. Furthermore, some patients receiving care in the ED may not have regular providers or may be unable to schedule a timely visit with a provider before a prescription runs out, and thus may be lost to follow-up.

Postoperative pain requirements may be different for similar procedures performed as inpatient versus outpatient. For example, patients undergoing knee arthroplasty with a planned inpatient stay, during which both intravenous and oral opioid regimens are given for postoperative pain control, may experience different pain management than patients undergoing knee arthroplasty as an outpatient procedure, for which postoperative prescribing must anticipate the potential pain a patient might experience at home when intravenous opioids are no longer available (Kelly et al., 2018).

Clinical Evaluation

Effective acute pain management requires first that a patient have timely access to a clinical evaluation for his or her pain. Prompt treatment of acute pain may help prevent additional morbidity or the development of chronic pain (Sinatra, 2010). However, patients may face a number of barriers to getting an evaluation, including a lack of health insurance coverage, few local providers being willing to accept a patient's insurance, delays for an appointment with a clinician, and logistical difficulties with keeping the appointment, such as a lack of transportation, difficulty in taking time off from work or school, and child care responsibilities.

A thorough clinical evaluation should include a review of a patient's medical record, including current and past medical illnesses; comorbidities; past medication history (particularly any history of substance misuse); and an assessment of the cause, site, severity, and impact of the pain. An assessment of comorbidities should also include an account of any psychological components, such as anxiety or depression, that may affect the symptoms of acute pain or that may influence a management plan (Michaelides and Zis, 2019). Historical patient information can be more easily accessed if a patient is returning to a clinician who he or she has seen previously for prior episodes of acute pain or other medical conditions, or if the clinician providing the evaluation of the acute pain incident has coordinated care with the patient's primary care and/or other health care providers to gather all relevant past and current medical information.

The committee recognizes that individual patients with an acute pain diagnosis will respond differently to treatment and there is variability in time to recovery. For example, Komatsu et al. (2017) found in a study of mothers after cesarean childbirth that it took 50 days, 24 days, and 43 days, respectively, for 95% of the women to achieve pain resolution, opioid cessation, and other analgesic cessation; these women had used opioids for a median duration of only 8 days (range 0–39). The median time to "pain and opioid-free functional recovery" was 27 days, but there was a broad range of 19–40 days. This study demonstrates that while pain is an important factor in functional recovery, there is a highly variable trajectory for each outcome (e.g., pain, functional recovery, opioid use, and other analgesic use) and opioid use resolution precedes analgesic resolution.

Patients with ongoing pain that lasts beyond the expected recovery period will require re-evaluation for adequate pain control. They need timely access to a clinician who can assess their pain, determine whether additional medication is necessary or an alternative treatment strategy is warranted, and determine whether further evaluation is indicated for the persistent pain. The goals for patients with ongoing

acute pain is to manage the pain and prevent both chronic pain and long-term treatment with opioids. Therefore, continuous monitoring of the patient's treatment and recovery is essential to ensure that the appropriate amounts of opioids are prescribed in conjunction with other treatment modalities.

Pain Management Strategies

Patients with acute pain may be prescribed a variety of treatments, depending on the cause of the pain and the patient's history. Initial treatments may include nonpharmaceutical interventions (e.g., physical therapy, ice, and immobilization), nonopioid analgesics, or a combination of nonopioid treatments. If these approaches are effective in relieving the acute pain within the projected healing period for that condition, opioids may not be necessary.

Since the 1990s anesthesiologists and surgeons have collaborated to enhance recovery from surgical procedures, but their initial efforts were not always focused on reducing opioid use per se. Instead, programs were developed to expedite discharge from the hospital or to convert previous overnight or multiday hospital stays into ambulatory surgical experiences. More recently it has been recognized that the overall opioid burden after surgery can be reduced by programs such as enhanced recovery and implementing the wider use of nonopioid and multimodal analgesia (Jandali et al., 2019; Simpson et al., 2019). Furthermore, chronic relapses of painful diseases, such as sickle cell anemia, can be more effectively managed with opioid sparing techniques. These initiatives have resulted in reducing, but not necessarily eliminating, the need for outpatient opioid prescribing.

Prompt Access to Pain Management Interventions

After the patient receives his or her treatment recommendations, referrals, and prescriptions, other factors will affect the patient's ability to implement pain management. For instance, various factors that may affect a patient's access to care must be considered, including pharmacy access, health insurance guidelines and restrictions, and state laws limiting opioid prescriptions.

Health insurance coverage of nonopioid treatments is not always consistent with clinical standards, whereas opioids are commonly covered (Becker et al., 2017; Simmonds et al., 2015; Weeks, 2016). For example, a 2018 review of insurance coverage for nonpharmacologic treatments for low back pain found that physical and occupational therapy and chiropractic care were covered by about 90% of all of the insurance plans examined but that other nonpharmacologic treatments, such as psychological interventions, transcutaneous electrical nerve stimulation, and acupuncture, were not covered or were only partially covered (Heyward et al., 2018). Huskamp et al. (2018) studied 100 plans offered on the 2017 Health Insurance Marketplaces, with a randomly selected plan from a rural county and an urban county in each state; 100% of these plans covered at least short-acting opioid pain medication.

People without health coverage are less likely to obtain recommended treatments than those with coverage (Garfield et al., 2016). Some health insurers require that clinicians adhere to opioid prescribing rules. For example, Medicare requires that prescribers conduct opioid pain medication safety checks, get prior authorization, limit quantities, and use step therapy. Also, Medicare might not cover some drugs provided to patients in hospital outpatient settings, such as EDs (CMS, 2019). Prescribers may request exemptions for their patients as necessary, but this may prevent prompt access to opioids for acute pain.

Other barriers that may impede access to acute pain treatment include the lack of access to a conveniently located pharmacy or other treatment facilities (e.g., physical therapy clinic); a patient's inability to pay for his or her prescriptions, including copays; and a patient's inability to attend timely follow-up appointments. The latter barrier may occur for a variety of reasons such as difficulty in taking time off

work or school, poor access to transportation, living in a long distance from a health care facility, and the need for child care during the patient's appointment. Health care providers may prescribe for their patients under the assumption that patients have equal access to care at the point of prescribing and that patients in pain have sufficient opportunity to fill the prescription (e.g., prescription drug coverage, access to a pharmacy that stocks opioids).

Patients also need access to a pharmacy that is appropriately stocked in order to fill an opioid prescription. A review of community pharmacies between 2007 and 2015, found that there was significant variation in the number of pharmacies per capita at the county level, that pharmacies are not distributed equally based on population, and that other factors also varied, including hours of operation, and the availability of home delivery service, multilingual staff, a drive-up window, and e-prescription options (Qato et al., 2017). Jefferson et al. (2019) found that 50% of patients who identified as black and who had a cancer diagnosis had difficulty obtaining opioids from a neighborhood pharmacy, primarily because the drugs were not in stock. An earlier study found that only 25% of pharmacies in predominantly nonwhite neighborhoods had sufficient opioid supplies to treat patients in severe pain, as compared with 72% of pharmacies in predominantly white neighborhoods ($p<0.001$) (Morrison et al., 2000). Some patients may live a considerable distance from a pharmacy (e.g., a rural area), requiring lengthy travel to fill a prescription. All of these factors can affect a patient's ability to maintain a pain management regime. Bissonnette et al. (2016) found that home delivery and drive-up options may be especially important for elderly populations and that multilingual staff are essential for ensuring that non-English speaking patients are able to receive proper instructions on how to take prescribed opioid or nonopioid analgesics.

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3

Development and Use of Clinical Practice Guidelines

The 2011 Institute of Medicine (IOM) report *Clinical Practice Guidelines We Can Trust* defined clinical practice guidelines (CPGs) as "statements that included recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms or alternative care options" (IOM, 2011a, p. 4). Evidence-based practice is the integration of the best research evidence, clinical expertise, and patient values into the decision-making process for patient care (IOM, 2008; Straus et al., 2019). Thus, CPGs are intended to synthesize the available evidence and knowledge in order to create pragmatic tools for clinicians to optimize care for patients with specific medical conditions or undergoing specific surgical procedures. A trustworthy CPG can help clinicians and patients improve their communications and decision making about the risks and benefits of clinical activities, including treatments and diagnostic procedures, and can improve the safety and effectiveness of those treatments and procedures (Dowell et al., 2016). In particular, the consistent use of CPGs can help clinicians reduce inappropriate prescribing of opioids (Bohnert et al., 2018).

CPGs are used in a variety of setting and by a range of clinicians who prescribe opioids as well as by other health care professionals involved in the management of acute pain. Other users of CPGs can include health insurers; regulatory agencies at the federal, state, and local levels; and pharmacy benefits managers aiming to identify and promote best practices in pain management. Finally, CPGs are of value to patients, caregivers, and advocates for setting expectations for recovery and providing education on the safe use of opioid and nonopioid analgesics. CPGs may be used by clinicians in a variety of clinical settings; consistent with its charge, the committee focused on those settings where opioid prescriptions are written, including primary care clinics, emergency departments (EDs), dental clinics, medical specialty clinics, and ambulatory surgical facilities.

Although many guidelines are publicly available, some that have been developed by professional societies may not be widely available. The committee notes that until 2018, the Agency for Healthcare Research and Quality (AHRQ) maintained the National Guidelines Clearinghouse. Created in 1997 by AHRQ in partnership with the American Medical Association and the American Association of Health Plans (now America's Health Insurance Plans [AHIP]), the publicly available website provided physicians, other health care professionals, health care systems, and others with objective, detailed

information on CPGs to promote their dissemination, implementation, and use (AHRQ, 2018). With the defunding of the clearinghouse in 2018, the guidelines it contained are no longer publicly available through AHRQ, although some of them may be available from the original source. As of October 2019, AHRQ stated that it is conducting a study to identify new models for disseminating and accessing CPGs. In this report, the committee focused on CPGs that are publicly available.

PRINCIPLES OF CLINICAL PRACTICE GUIDELINE DEVELOPMENT

The development of trustworthy and useful evidence-based CPGs requires a standardized process. As discussed in the 2011 IOM report *Clinical Practice Guidelines We Can Trust*, transparent and consistent processes can increase the trust in, uptake of, and adherence to a CPG. Many health care organizations not only have created CPGs, but also have established protocols or manuals for the development of CPGs within their specialty areas. Among the organizations that have created such guideline development manuals are the American Academy of Audiology, the American Physical Therapy Association, and the Council of Medical Specialty Societies (CMSS).

Clinical Practice Guideline Development Criteria

High-quality guidelines follow the best-practice guideline development criteria established by the IOM (2011a). The criteria for such guidelines include

- a complete description of development, sponsorship, and funding processes that are transparent and accessible;
- a transparent process that acknowledges and minimizes the potential for bias and conflicts of interest;
- input from stakeholders and experts across multiple disciplines, including representatives of patients who will be affected by the guideline;
- a rigorous systematic review of the current evidence and an assessment of the quality, quantity, and consistency of this evidence;
- a summary of the evidence and gaps in knowledge regarding the potential benefits and harms relevant to each recommendation;
- a disclosure of recommendations that are based on values, opinions, theories, and clinical experiences and a rating of the strength of each recommendation is included based on the available evidence and panel consensus;
- an external peer and public review and public comment process;
- a mechanism for revision when new evidence becomes available; and
- a process for guideline adoption, dissemination, and implementation.

The systematic reviews on which CPGs are based also need to be conducted in a standardized manner to ensure that the evidence accurately supports any recommendations based on that evidence (IOM, 2011a). Several organizations have developed methodologies for systematic reviews, including IOM (2011b), Cochrane (Higgins et al., 2019), and AHRQ (2018b). The IOM (2011b) recommended four broad standards for synthesizing the body of evidence:

- Use a prespecified method to evaluate the body of evidence;
- Conduct a qualitative synthesis;

- Decide if, in addition to a qualitative analysis, the systematic review will include a quantitative analysis (meta-analysis); and
- If conducting a meta-analysis, use expert methodologists, address heterogeneity among study effects, include measures of statistical uncertainty with all estimates, and conduct sensitivity analyses.

Strengths and Limitations of Clinical Practice Guidelines

Trustworthy CPGs provide clinicians, policy makers, and other stakeholders with tools to guide evidence-based practice decisions for the care of patients in specified clinical circumstances. The purpose of guidelines is to help clinicians translate current research in basic science and diagnostic and therapeutic interventions into clinical practice in order to improve the clinical outcomes (Linda et al., 2013; Murad, 2017). The volume of research on opioids for a number of surgical and medical indications is growing daily, and it is difficult, if not impossible, for clinicians to stay informed on and synthesize all of the latest literature into their practice. CPGs provide clinicians with recommendations on opioid prescribing for acute pain based on the latest and best available evidence in order to improve short- and long-term health outcomes, reduce the number of unused pills, reduce the need for refills, and inform the appropriate use of nonopioid medications and nonpharmacologic therapies. Another strength of CPGs is that they can provide treatment recommendations for specific subpopulations, such as patients with physical or mental health comorbidities, children or the elderly, patients who are currently taking opioids for a chronic condition, and patients with substance use or opioid use disorder.

Despite the recognized merits of CPGs, they do have limitations. First, CPGs are often limited in the extent to which they address the individualization of therapy based on patient, setting, clinician, and other factors, frequently because of a lack of evidence. Second, the impact of CPGs may be limited due to low uptake by clinicians and policy makers. Third, the implementation of CPGs may result in unintended consequences. For example, the 2016 Centers for Disease Control and Prevention (CDC) guideline on opioid use for chronic pain has been applied to patients with active cancer pain and has been used to support policies for mandatory opioid tapering—even though the guideline explicitly states that it is not intended for patients with active cancer pain and does not recommend tapering in all patients (Dowell et al., 2019; Kroenke et al., 2019). Finally, the publication of new evidence can make CPGs outdated, particularly for recommendations supported by low-quality evidence (Shekelle, 2014).

Several strategies are used by CPG developers to address these challenges. To facilitate greater individualization of therapy, CPGs can explicitly consider patient, setting, clinician, and other factors that affect response to therapy, to the extent possible. When evidence is lacking with which to guide individualization of therapy for certain subgroups (e.g., patients with history of opioid use disorder), CPGs can acknowledge the evidence gaps and indicate situations in which deviation from recommendations may be warranted.

Scope of Clinical Practice Guidelines

CPGs differ in scope. Some are broad in scope and describe how to prescribe opioids for a general medical indication; these include the American College of Occupational and Environmental Medicine's (ACOEM's) *ACOEM Practice Guidelines: Opioids for Treatment of Acute, Subacute, Chronic and Postoperative Pain* (ACOEM, 2014), the joint American Pain Society and American Academy of Pain Medicine's 2009 *Clinical Guidelines for the Use of Chronic Opioid Therapy for Chronic Noncancer Pain*, and the 2016 *CDC Guideline for Prescribing Opioids for Chronic Pain.* Other CPGs may be relatively

narrow in focus and provide recommendations for the treatment of a specific population or surgical or medical indication, such as the *Consensus Statement for the Prevention and Management of Pain in the Newborn* (Anand and the Internal Evidence-Based Group on Neonatal Pain, 2001). The variation in scope may be the result of differing missions and goals among the authoring organizations as they seek to address the needs of their members, patient populations, and clinical specialties; resource constraints; and the availability of scientific evidence.

Guidelines that are intended to help clinicians manage acute pain may also include recommendations for chronic pain, general pain, or pain resulting from specific causes, such as surgery, dental treatments, or cancer. Furthermore, not all guidelines for pain management are specific to opioid prescribing, and some may address other treatments such as nonopioid pharmacotherapeutics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], gabapentinoids, and steroid injections) and nonpharmacologic therapies (e.g., physical therapy, heat, acupuncture, and chiropractic care).

METHODOLOGIES FOR DEVELOPING CLINICAL PRACTICE GUIDELINES

Numerous organizations have proposed standardized, transparent methodologies for CPG development with the aim of producing more trustworthy and accepted documents. Several organizations, including the IOM; the U.S. Preventive Services Task Force (USPSTF); the Appraisal of Guidelines, Research and Evaluation (AGREE) Collaborative; the U.S. Department of Veterans Affairs (VA) in collaboration with the U.S. Department of Defense (DoD); and the UK National Institute for Health and Care Excellence, have published methodologies for establishing rigorous approaches to the development of guidelines. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group is a resource for quality assessment of evidence and guidelines. Many medical and other health care professional societies also have standardized methods for producing CPGs. In some cases, the description of methods for developing the guidelines is brief and details regarding the criteria used to grade or rate the scientific strength of studies may be lacking (e.g., American Academy of Audiology, 2006), whereas others are based primarily on the precepts advanced by the IOM, GRADE, or other organizations (e.g., American Academy of Family Physicians, 2017). Organizations such as CMSS, the American College of Cardiology Foundation, and the American Heart Association Task Force on Practice Guidelines oversee and direct the CPG development processes and have standardized methodologies to do so. The World Health Organization (WHO) provides a handbook on guideline development that incorporates GRADE for evaluating the quality of evidence.

The committee briefly summarizes these various methodologies below.

Institute of Medicine

Building on work done by the IOM in the early 1990s (IOM, 1990, 1992, 1995), in 2010 the U.S. Department of Health and Human Services asked the IOM to further examine what might be done to improve the impact that CPGs have on clinical practice and also to examine the research on which they are based. The resulting 2011 IOM report, *Clinical Practice Guidelines We Can Trust*, laid out a number of criteria that, if addressed, would be expected to produce high-quality and trustworthy CPGs that could help enhance the translation of research, particularly randomized controlled trials, into better clinical decisions and ultimately improve patient care. The IOM report recommended eight standards for developing CPGs (see section on Clinical Practice Guideline Development Criteria). Thus, the IOM report addresses composition of the guideline development group, management of conflicts of interest,

decision-making processes, evidence synthesis, and reporting of recommendations, among other important aspects of GPG development.

The IOM committee acknowledged that even the most trustworthy and scientifically valid CPG must be used at the clinician level to be effective. To that end, the report recommended that CPGs should be structured "to facilitate ready implementation of computer-aided CDS [clinical decision support] by end-users" (p. 13). The IOM further stated that transparency in how the methods were actually applied and in the choices made is critical for developing high-quality systematic reviews of comparative effectiveness research.

In a 2011 companion report, *Finding What Works in Health Care: Standards for Systematic Reviews*, the IOM described the advantages of a systematic review versus a narrative review (IOM, 2011b). Systematic reviews use a predetermined set of criteria that are intended to reduce bias in the identification, selection, assessment, and synthesis of information from similar but separate studies. Systematic reviews may be either qualitative or quantitative; a systematic review may also include a meta-analysis, that is, a statistical analysis of the data from several studies. A meta-analysis may inform clinical decision making for a CPG (IOM, 2011b), help estimate the statistical heterogeneity among studies, and highlight factors that affect different estimates of the harms and benefits of a particular clinical practice (Chou, 2008). The IOM proposed 21 standards with 82 elements across the systematic review process, from formulating the topic to developing a final systematic review report.

Grading of Recommendations Assessment, Development and Evaluation

The GRADE Working Group, based at McMaster University in Canada, developed the GRADE approach to rating the quality of evidence that supports the development of CPGs and grading the strength of recommendations based on that evidence (Siemieniuk and Guyatt, 2019). This approach is widely used by health care organizations, ranging from CDC to professional societies. The integral aspects of the GRADE approach are the production of evidence profiles, systematic reviews, a summary of findings tables, and graded recommendations using a GRADEpro computer program. Beginning in 2011, the GRADE Working Group has published numerous articles that detail the methodology of the approach so that guideline developers may use it to produce high-quality CPGs. The articles cover how to rate the quality of evidence in terms of bias, precision, consistency, directness; how to summarize the evidence for individual, binary, and continuous outcomes; how to apply GRADE to diagnostic tests; how to move from evidence to recommendations; and the challenges of using observational studies (Guyatt et al., 2011).

U.S. Preventive Services Task Force

The USPSTF is a volunteer panel of 16 experts in prevention and evidence-based medicine who convene to systematically review evidence to make recommendations about clinical preventive services in asymptomatic persons, such as screening for breast cancer or for abdominal aortic aneurysms (USPSTF, 2018a). The USPSTF guidelines do not provide recommendations for treating populations undergoing surgical procedures or who have medical conditions, although the guidelines may recommend how the preventive services may need to be tailored for such populations. The standards for guideline development closely align with those delineated in the IOM 2011 report (USPSTF, 2018b). The USPSTF published its procedure manual in 2015 to describe its process for selecting topics, reviewing evidence, and arriving at recommendations (USPSTF, 2018a). Some important aspects of the USPTSTF method that distinguishes it from other CPG development methods is the consideration of indirect pathways

and chains of evidence and the use of analytic frameworks, key concepts for this report as discussed in Chapter 4.

To describe the strength of each recommendation and balance the harms and benefits associated with it, the USPSTF developed grade definitions ranging from A (recommends this service and there is high certainty that the net benefit is substantial) to D (recommends against this service and there is moderate or high certainty that the service has no net benefit) (USPSTF, 2018a). When evaluating indirect evidence, observational data, and studies with intermediate endpoints as outcomes, the USPSTF uses the criterion of coherence to assess the certainty of indirect evidence, extrapolation to estimate the magnitude of the net benefit, and conceptual bounding to estimate the theoretical lower or upper limits of the net benefit (Krist et al., 2018). Evidence gaps and special populations are also identified and considered in the evaluation process (Bibbins-Domingo et al., 2017; Kemper et al., 2018; Whitlock et al., 2017). The complete list of USPSTF recommendations is publicly available online.

Other Methodologies

Other organizations have developed methodologies that facilitate CPG development or assessment. These organizations include the AGREE II Collaboration and AHRQ.

AGREE has developed an instrument and user's manual to "assess the process of guideline development and reporting of this process in the guideline" (Brouwers et al., 2010). The instrument comprises 23 items rated on a scale of 1 (strongly disagree) to 7 (strongly agree) grouped into six quality-related domains: scope and purpose; stakeholder involvement; rigor of development; clarity of presentation; applicability; and editorial independence.[1] Other countries such as Canada, France, and Germany have governmental organizations that develop and disseminate systematic reviews and CPG guidance; international organizations such the Health Technology Assessment International and Cochrane also develop and promote evidence-based assessments.

AHRQ established its Evidence-based Practice Center (EPC) program in 1997 to "develop evidence reports and technology assessments on topics relevant to clinical and other health care organization and delivery issues" and the Effective Health Care (EHC) program in 2005 to conduct systematic reviews (AHRQ, 2019). The reviews are performed by 14 EPCs that conduct comparative effectiveness reviews, effectiveness reviews, and technical briefs that are focused on patient-centered outcomes. The AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (2008) guides the EHC program's systematic reviews with the goal of making the health care information accessible to patients, clinicians, and policy makers. The AHRQ guidance contains many standards identified by the IOM reports on systematic reviews and the development of CPGs, including disclosure of competing interests by developers, extensive training for the review team, the use of key questions to guide the review process, and the posting of draft materials at several stages of the development process in order to seek public input. AHRQ also provides guidance on conducting comparative effectiveness reviews on the relative benefits and harms of a range of options, which addresses interventions beyond whether one particular treatment is safe and effective.

[1] All AGREE II information is publicly available from http://www.agreetrust.org, including an online training tool for using the instrument.

EXAMPLES OF OPIOID PRESCRIBING GUIDELINES FOR ACUTE PAIN

There are a vast number of guidelines[2] for managing pain, including for the use of opioids for acute and chronic pain, offered by different organizations, ranging from federal government agencies to state legislatures to professional societies and even individual health care institutions. Often, CPGs are issued by clinical professional societies, such as the American College of Physicians, the American Academy of Orthopaedic Surgeons, and the American Urological Association; however, CPGs have also been issued by federal agencies, such as the VA/DoD *VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain* (2017). The committee notes that in addition to CPGs on opioid prescribing, there are other types of recommendations for clinicians, including practice guidelines based on consensus rather than evidence; policies and recommendations from health care organizations or departments, consortia of health care organizations, governmental agencies such as CDC, state and local agencies such as state medical boards and municipal health departments, and health insurers; as well as state laws on opioid prescribing. Other organizations have developed documents similarly intended to provide clinical recommendations, such as the 2017 American Association of Oral and Maxillofacial Surgeons' white paper *Opioid Prescribing: Acute and Postoperative Pain Management*, but these documents lack key elements of evidence-based CPGs (see Chapter 4). Several states have also developed guidelines for opioid prescribing, for example, the *Minnesota Opioid Prescribing Guidelines, First Edition, 2018*, and the Michigan Opioid Prescribing Engagement Network's *Opioid Prescribing Recommendations for Opioid-Naïve Patients* from 2018. Based on the breadth of CPGs for opioid prescribing, the committee considered these and other types of guidance documents for surgical procedures and medical conditions. The latter may not meet the criteria for a CPG, defined as guidance based on a formal evidence review with rating of the evidence using a prespecified rating scheme. However, the committee uses the term "guidelines" to refer to the entire range of recommendations on opioid prescribing for acute pain.

Selected examples of guidelines developed by a variety of organizations are summarized briefly below.

Federal Government Agencies

Several federal government agencies have produced guidelines and implemented policies to address the opioid epidemic, most notably CDC and VA/DoD. Those guidelines are not indication-specific, but rather aim to address opioid prescribing and pain management for both acute and chronic pain. Examples of those CPGs are summarized below:

- CDC developed and published the *CDC Guideline for Prescribing Opioids for Chronic Pain* in 2016 (Dowell et al., 2016). While focused primarily on chronic pain, the guideline also addresses acute pain and recommends that clinicians prescribe a quantity no greater than what is needed for the expected duration of pain severe enough to require opioids, specifying that 3 days or less will often be sufficient and that more than 7 days will rarely be needed for acute pain indications. The CDC guideline also addresses dose-dependent risks of opioids. This guideline has become the basis for many other stakeholders' guidelines, including many state prescribing limits (see section on State and Local Governments).
- The 2017 *VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain*, while focused on opioids for chronic pain, also includes recommendations on their use for acute pain.

[2] Though there are numerous CPGs and other guidelines offered by other countries, including Australia, Canada, and the United Kingdom, the committee did not review them or consider them for its task, given the different medical systems and prescribing environments.

Specifically, the guideline recommends "against prescribing long-acting opioids for acute pain, as an as-needed medication, or on initiation of long-term opioid therapy" (VA/DoD, 2017, p. 8). The recommendations for using opioids to treat acute pain range from strong (use alternatives to opioids for mild to moderate acute pain) to weak (use mulitmodal pain care when using opioids). This VA/DoD CPG is evidence based and follows the *VA/DoD Guideline for Guidelines* (VA/DoD, 2019). The guideline uses the GRADE approach to assess the quality of the evidence and assign a rating for the strength of each recommendation.

- The Centers for Medicare & Medicaid Services has issued opioid policy guidelines that include safety alerts at pharmacies for initial opioid prescriptions or high doses as well as an adjustment to the default fill of prescription opioids for acute pain for opioid-naïve patients to 7 days for Medicare Part D programs. The policy recommends that states block payment for opioid prescriptions of more than 7 days or more than 90 morphine milligram equivalents (MMEs) (Brandt, 2019; CMS, 2018) (see section on Health Care Systems and Health Insurers).

Professional Societies

The 2011 IOM report has been used by numerous medical specialty societies and other health care organizations as the basis for creating their own CPG development processes and methodologies, manuals, and guidelines (e.g., APTA, 2018; CMSS, 2017). Medical specialty and professional societies offer an abundance of Web-based patient care guidelines for pain management that focus on opioid prescribing, with many of them publicly available. For example, the American Academy of Emergency Medicine has developed a White Paper Position Statement on the Treatment of Acute Pain in the Emergency Department (Motov et al., 2018) and the American Society of Anesthesiologists *Practice Guidelines for Acute Pain Management in the Perioperative Setting* (ASA, 2012). Some examples of other guidelines developed by medical specialty societies are briefly discussed below (other guidelines for priority surgical and medical indications are presented in Chapter 5, Tables 5-2 and 5-3, respectively):

- In 2016 ACOEM released a guideline statement titled *Principles for Ensuring the Safe Management of Pain Medication Prescriptions by Occuptational and Environmental Medicine Physicians* (Mueller et al., 2016). It lists selected measures from ACOEM's *Occupational Medicine Practice Guidelines* to decrease harmful opioid use for chronic noncancer pain as well as one bullet about prescribing for acute pain:

  > When prescribing opioids for acute pain, physicians should set expectations for discontinuation, and limit quantities of prescriptions to what is clinically needed. In most non-operative cases opioids should be limited to several days, preferably less than a week and not to exceed 2 weeks. (ACOEM, 2011)

- The American College of Obstetricians and Gynecologists (ACOG) has opioid-related guidance and resources for providers on its website (ACOG, 2019). These range from a webinar titled *Maternal Transitions in Care for the Mother–Infant Dyad Affected by Opioid Use Disorder* to *Guidelines for Perinatal Care, 8th Edition*, which was developed jointly with the American Academy of Pediatrics in 2017 and includes a brief guideline regarding prescribing opioids for acute pain. The ACOG Commitee on Obstetric Practice (2018) also released an opinion regarding presribing opioids for postpartum pain management. The ACOG practice bulletins are similar to CPGs, although they are not publicly available; committee opinion documents, however, which also include recommendations but are less rigorous than CPGs, are publicly available.

- In 2018 the American Dental Association (ADA) updated its policy on the use of opioids to treat dental pain and emphasized using nonopioids as the first-line therapy for acute dental pain. ADA supports statutory limits on opioid dosage and a duration of no more than 7 days for acute pain treatment (ADA, 2018). The American Academy of Pediatric Dentristy released a policy statement titled *Policy on Acute Pediatric Dental Pain Management* in 2017, that offers guidelines for prescribing opioid anelgesics for pediatric patients (AAPD, 2017).
- The Society for Pediatric Anesthesia recently released an evaluation of the available literature on the use of opioids in children during the perioperative period and formulated recommendations. The recommendations were graded based on the strength of the available evidence using the three-tiered classification system developed by the American Society of Anesthesiologists. For issues in which evidence was unavailable, expert consensus was used. Recommendations were made concerning opioid administration to children after surgery, including appropriate assessment of pain, as well as the monitoring of patients on opioid therapy, opioid dosing considerations, the side effects of opioid treatment, strategies for opioid delivery, and the assessment of analgesic efficacy (Cravero et al., 2019).

Health Care Systems and Health Insurers

Numerous health systems, large and small, for-profit and not-for-profit, have been involved in the development and implementation of guidelines for prescribing opioids. Health care systems such as Kaiser Permanente, the Mayo Clinic, and Intermountain Healthcare have adopted prescribing guidelines. Two examples are described briefly below:

- The Massachusetts Health & Hospital Association (MHA) and the Tufts Medical Center released a CPG in June 2018 titled *Inpatient Opioid Misuse Prevention: A Comprehensive Guide for Patient Management with Regards to Opioid Misuse*. MHA's Substance Use Disorder Prevention and Treatment Task Force also published *Guidelines for Prescription Opioid Management within Hospitals* and *Guidelines for Emergency Department Opioid Management*.
- The Mayo Clinic used its patient datasets to develop internal opioid prescribing guidelines for its Department of Orthopedic Surgery in 2017. Three opioid dose levels (low, standard, high) are used depending on the severity of the condition and the surgical procedure. Subsequently Mayo developed its clinical surgical outcomes program recommendations for adult discharge opioid pescriptions for a number of surgical procedures across eight surgical specialties. Clinicians were cautioned, however, that the recommendations—which included recommendations on low, standard, and high dose prescribing for both opioids and nonopioids—did not supersede clinical judgment or department-level guidelines (Elizabeth Habermann, Mayo Clinic, presentation to committee, July 9, 2019).

Other stakeholders, including electronic health record (EHR) companies and health insurers, have also tried to address opioid misuse and overprescribing in response to the opioid epidemic. Studies have shown an association between lower prescription default values for postoperative opioids in EHRs and reduced clinician prescribing practices (Delgado et al., 2018). For example, lowering the EHR default from 30 pills to 12 pills decreased the amount of opioids prescribed by more than 15% across an entire health system (Chiu et al., 2018). The Electronic Health Record Association Opioid Crisis Task Force is examining how to best use EHRs to fight the opioid epidemic. The association published an EHR

implementation guide for the CDC CPG. In response to the CDC CPG, Epic Systems[3] set its defaults for opioid prescribing based on the CDC prescription limits (Donovan, 2018). The Pharmaceutical Research and Manufactuters of America, which represents several opioid manufacturers, including Bayer, Pfizer, and Merck, announced its support for limiting the supply of opioids to 7 days for acute pain management (PhRMA, 2017). AHIP, a national association of health insurers, announced its Safe, Transparent Opioid Prescribing initiative "to support widespread adoption of clinical guidelines for pain care and opioid prescribing" (AHIP, 2019). AHIP noted that many of its member health insurers are working with federal and state agencies, doctors, and hospitals to reduce inappropriate opioid prescribing and promote the use of effective, alternative treatments for pain.

State and Local Governments

All 50 states as well as the District of Columbia have some form of opioid prescribing guidelines, which can range from advisory guidelines to legally binding limits on opioid prescribing.[4] In 2016 Massachusetts was the first state to pass a law limiting first-time opioid prescriptions to 7 days. Since then more than half of all states have enacted laws that restrict the prescribing or dispensing of opioids for acute pain (Davis et al., 2019; NCSL, 2018) (see Figure 3-1). Most state restrictions have established a limit on the number of days' supply of the drug or a daily MME limit or both. For example, Virginia both regulates the number of days for an opioid supply and imposes a dosage limit; that is, the prescription may not be longer than 7 days, or 14 days for a postsurgical procedure, and unless "extenuating circumstances" are documented by the clinician in the patient's medical records, the dosage cannot exceed 50 MME/day.[5] Maryland restricts prescriptions to the "lowest effective dose" but does not specify a day limit (Davis et al., 2019). Many states also set limits specifically for minors (NCSL, 2018).

Some states emphasize the need for medical education concerning the prescription of opioids. For example, Arizona limits the number of days' supply of opioids and the MME/day. It also requires 3 hours of opioid continuing medical education for physicians with a Drug Enforcement Administration registration number and 3 hours of education about opioids for medical students (Arizona, 2018).

State agencies, in collaboration with other organizations, have also issued procedure-specific opioid prescribing guidelines. In 2015 the Washington State Agency Medical Directors' Group, in collaboration with the Dr. Robert Bree Collaborative and an advisory group of the state's academic leaders, pain experts, and surgeons, created the evidence-based *Supplemental Guidance on Prescribing Opioid for Postoperative Pain* and *Dental Guideline on Prescribing Opioid for Acute Pain Management* (Washington State Agency Medical Directors' Group, 2019). The Michigan Opioid Prescribing Engagement Network—a public–private collaborative that receives support from the State of Michigan as well as federal funding sources—has developed procedure-specific opioid prescribing recommendations for patients undergoing 25 common surgical procedures such as dental extraction, appendectomy, and laparoscopic cholecystectomy (Michigan OPEN, 2019).

[3] Epic Systems is one of the largest providers of health information technology, used primarily by large U.S. hospitals and health systems to access, organize, store, and share electronic health records.

[4] See Corey Davis, *The Network for Public Health Law Southeastern Region Office & the National Health Law Program, Appendix B, State-by-State Summary of Opioid Prescribing Regulations and Guidelines*, at http://www.azdhs.gov/documents/prevention/womens-childrens-health/injury-prevention/opioid-prevention/appendix-b-state-by-state-summary.pdf (accessed August 5, 2019).

[5] See Va. Admin. Code §§ 85-21-10–170, available at http://register.dls.virginia.gov/details.aspx?id=6295 (accessed August 5, 2019).

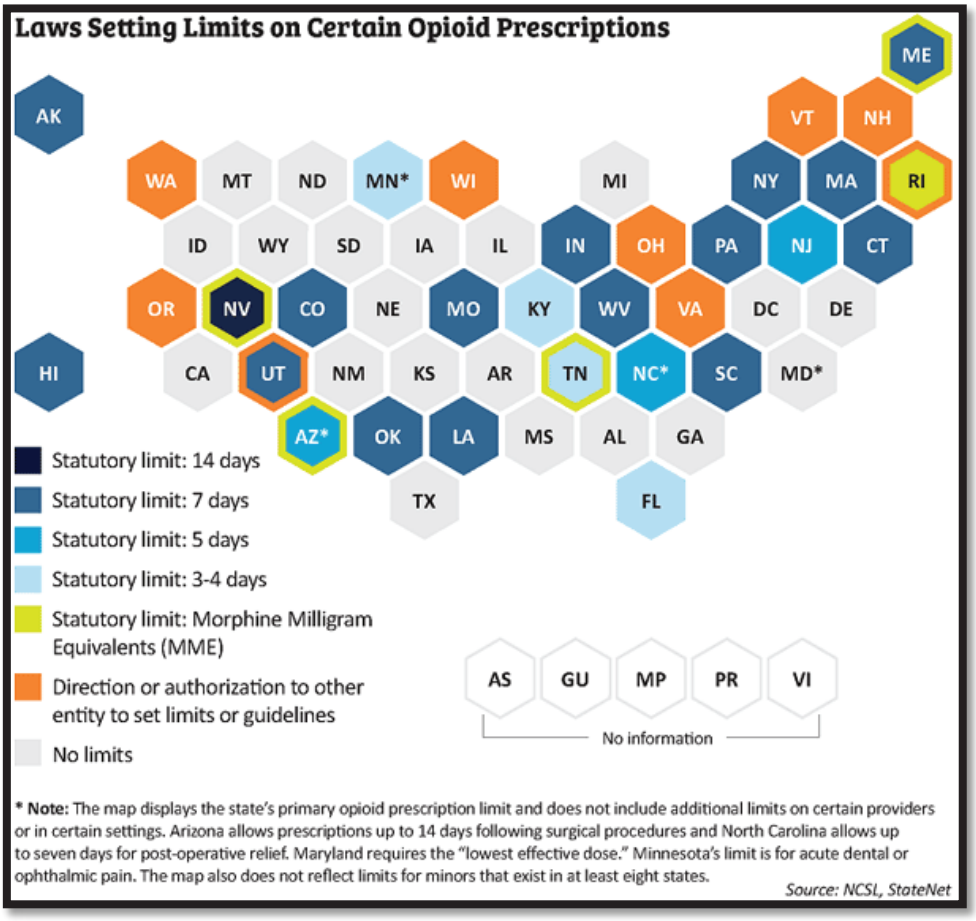

FIGURE 3-1 Legislation enacted by all 50 states with a limit, guideline, or requirement related to opioid prescribing, as of October 2018.
SOURCE: National Conference of State Legislators, StateNet (with permission).

Several states have used the CDC CPG for chronic pain[6] as a model for their opioid guidelines. For example, the Oregon Health Authority publication *Oregon Acute Opioid Prescribing Guidelines: Recommendations for Patients with Acute Pain Not Currently on Opioids*, used the CDC CPG as the starting point (Oregon Health Authority, 2016), and Alaska, Connecticut, and Kentucky explicitly referenced the CDC CPG in their laws (Davis et al., 2019).

A few states (e.g., New Hampshire, Ohio, Vermont, Virginia, Washington, and Wisconsin) authorize state entities to determine opioid prescribing limits. These entities may include departments of health, state and public health officials, or state boards of medicine, nursing, and dentistry. As state medical boards are the primary regulatory authority governing physicians who prescribe opioids, there is an incentive for state legislatures and state medical boards to work in tandem to craft opioid prescribing guidelines. Most of the state medical boards that provide guidelines recommend that nonopioid or nonpharmacologic pain management strategies be considered prior to initiating opioid therapy and that opioids be prescribed in limited amounts and doses consistent with the expected clinical course of pain (NASEM, 2017).

[6] Most states specifically set exceptions for prescription limits for chronic pain treatment, cancer treatment, and palliative care, similar to the CDC guideline.

Along with prescribing limits, some state legislation mandates the use of prescription drug monitoring programs (PDMPs),[7] which are electronic databases that track controlled prescriptions. Every state, other than Missouri, has a PDMP. PDMPs provide access to a patient's history of prescription opioids and help identify health care providers who prescribe high doses of opioids as well as patients who receive them. Evaluations of PDMPs have shown changes in prescribing behaviors, the use of multiple providers by patients, and decreased substance abuse treatment admissions (CDC, 2017). States have also issued policies mandating education for opioid prescribers as well as legislation requiring disclosure of the risks of opioid use and the importance of safe storage and disposal behaviors.

Local governments, including city health departments, have also issued opioid prescribing guidelines. For example, the New York City Department of Health developed opioid prescribing guidelines for primary care providers and then adapted these guidelines for ED discharge prescribing (Kattan et al., 2016; Nagel et al., 2018). The nine recommendations were modeled after the Washington State initiatives for regulating opioid prescribing that were intended to address the problem of excessive opioid prescribing in EDs (Chu et al., 2012; Juurlink et al., 2013). Among these recommendations are starting with the lowest dose of opioids, prescribing no more than a short course of opioids for acute pain (with more than 3 days rarely required), assessing patients for misuse or addiction, and avoiding initiating treatment with long-acting or extended-release opioids (Chu et al., 2012). The City of Philadelphia's Department of Public Health has also issued postoperative opioid prescribing guidelines that recommend opioid discharge prescription limits for opioid-naïve patients in any of 13 medical specialties (Philadelphia Department of Public Health, 2018).

Given the array of competing guidelines for treating pain, there is the potential for recommendations to overlap or be contradictory. This may be particularly true when state prescribing limits are discordant with prescribing recommendations developed by national professional societies, potentially resulting in confusion or the malalignment of practice.

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[7] See EHRA, *Prescription Drug Monitoring Programs & Electronic Prescribing of Controlled Substances* for a state-by-state summary of mandated PDMPs, at https://www.ehra.org/sites/ehra.org/files/EHRA%20PDMP%20-%20EPCS%20-%20State%20Landscape%20June%202018.pdf (accessed August 8, 2019).

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4

Framework for Developing Clinical Practice Guidelines

The 2011 Institute of Medicine (IOM) report *Clinical Practice Guidelines We Can Trust* states, "Clinical practice guidelines (CPGs) fundamentally rest on appraisal of the quality of relevant evidence, comparison of the benefits and harms of particular clinical recommendations, and value judgments regarding the importance of specific benefits and harms" (IOM, 2011a, p. 110). Effective and trustworthy CPGs are based on a rigorous review and analysis of the relevant scientific evidence (IOM, 1992, 2011a; Woolf et al., 2012). The review and analysis are parts of a guideline development process that begins with identifying the need for a guideline for a specific surgical or medical indication and then continues with the selection of guideline developers, gathering the scientific evidence, and, finally, approving, disseminating, and assessing the use of the guideline in a continuous quality improvement context (see Figure 4-1).

The development of CPGs is based on two frameworks: an analytic framework, which organizes the specific information required by a group to arrive at a recommendation, and an evidence evaluation framework, which describes the methods for assessing the quality of evidence and strength of recommendations. The implementation of these frameworks and the dissemination and use of CPGs after they are developed are also important steps in the CPG process. This chapter briefly addresses the entire CPG development process and provides a more in-depth discussion of the analytic framework and the evidence evaluation framework. It also considers how the use of CPGs by clinicians and other health care professionals might be enhanced.

As described in Chapter 3, numerous organizations have developed thoughtful, comprehensive, and widely used processes for developing CPGs. The committee considered that existing body of work when developing the two frameworks in this chapter, with a particular focus on the work by the IOM, the U.S. Preventive Services Task Force (USPSTF), the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, the Appraisal of Guidelines, Research and Evaluation (AGREE) Collaborative, and the Agency for Healthcare Research and Quality (AHRQ, 2015; Brouwers et al., 2010; Guyatt et al., 2008b; IOM, 2011a,b; USPSTF, 2018).

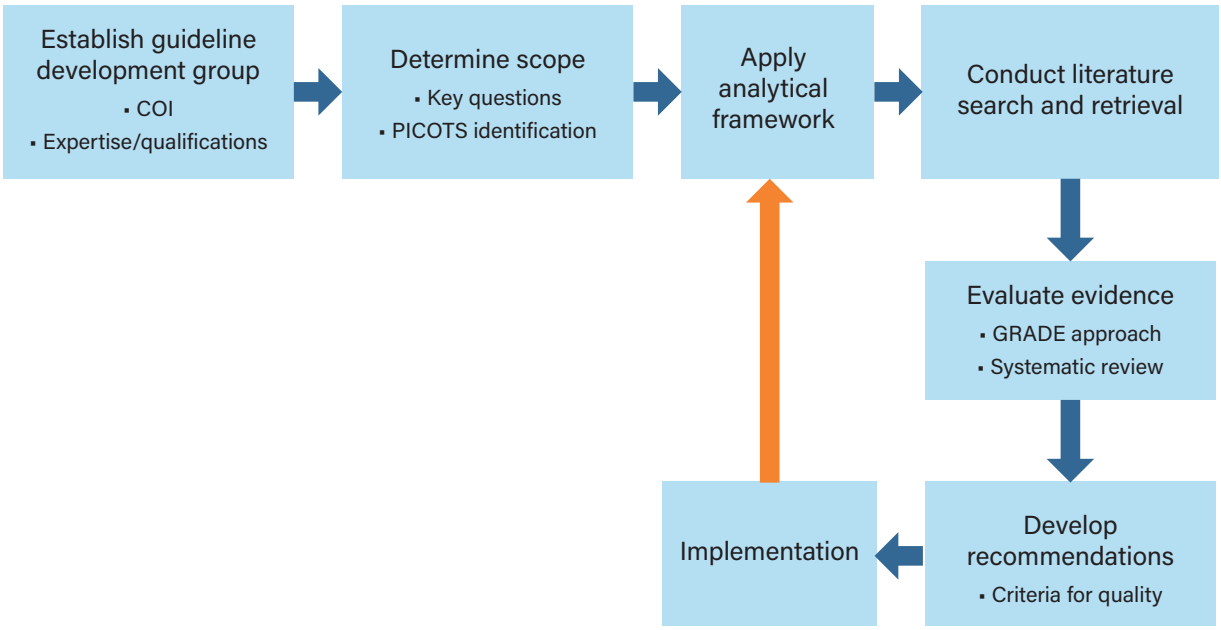

FIGURE 4-1 The evidence-based clinical practice guideline (CPG) development process. The orange arrow indicates where monitoring and assessment informs re-evaluation of the guideline and informs the feedback loop to periodically update the CPG based on new evidence as available.
NOTE: COI=conflict of interest; GRADE=Grading of Recommendations Assessment, Development and Evaluation; PICOTS=patient, problem, or population; intervention; comparison, control, or comparator; outcome; time; and setting.

In addition to the two frameworks, the committee also considered how CPGs for opioid prescribing might be used by clinicians. In the last section of this chapter, the committee briefly addresses four aspects of CPG implementation: dissemination, uptake, adherence, and monitoring outcomes.

THE CLINICAL PRACTICE GUIDELINE DEVELOPMENT PROCESS

The process for developing CPGs follows three core principles: (1) guidelines should be based on evidence that evaluates the efficacy or effectiveness of interventions on health outcomes, (2) guidelines should use the highest-quality evidence available, and (3) guidelines are developed for application to patient populations, but should allow for the individualization of care when possible (Balshem et al., 2011; Brouwers et al., 2010; Guirguis-Blake et al., 2007; IOM, 2011a; Nobrega et al., 2018; Radcliff et al., 2017; Rahim-Williams et al., 2007; Smith et al., 2019).

To address these core principles, the committee's overarching CPG development process provides a stepped process for assessing available evidence on opioid prescribing for acute pain indications, identifying research needs, and facilitating the incorporation of new knowledge into clinical practice as it becomes available (see Figure 4-1). Inherent in this process is the understanding that for many indications there are equal or superior nonopioid pain management strategies that might be considered and, in some cases, prescribed and used. However, for some medical indications of acute pain, such as

long bone fractures, sickle cell crisis, and many surgical procedures, initial therapy with a nonopioid or nonopharmacologic treatment may not be appropriate or feasible; for many indications, opioids are a recognized first-line treatment either alone (e.g., for femur fracture presenting in an emergency department [ED]) or in conjunction with nonopioid or nonpharmacologic treatments or both (Chou et al., 2016; Gross and Gordon, 2019; Motov et al., 2018). The committee recognizes that nonopioid modalities may be first-line treatments for some types of acute pain and that opioids may not be indicated for the management of acute pain for these conditions. However, the committee acknowledges that there are significant gaps in comparative studies examining opioid, nonopioid, and nonpharmacologic therapies, especially in perioperative pain management (Gordon et al., 2016).

ESTABLISHING A GUIDELINE DEVELOPMENT GROUP

CPGs with optimal impact are created with the end user and stakeholders (e.g., patients, insurers, ancillary health providers) in mind. To achieve this impact, guideline developers consider which health care professionals are most likely to care for such patients individually or as a part of a team—that is, the clinicians who will be using the CPG. CPGs may also address additional health care providers who are involved in a patient's care as well as the health care organizations that are key partners in the development process.

As discussed at some length in the 2011 IOM report *Clinical Practice Guidelines We Can Trust*, the first step in creating an evidence-based CPG is to identify and assemble a group of involved and interested experts who will develop it. Carefully selecting experts to ensure appropriate representation from all key stakeholders and health care providers and to include methodologists, epidemiologists, and statisticians will strengthens the developmental rigor and applicability of the evidence-based CPG (IOM, 2011a). Moreover, given the importance of social determinants of health (see Chapter 3) and the national impact of the opioid epidemic, it is desirable to ensure diversity among the guideline developers with regard to race, gender, age, and geographic location. The 2011 IOM report on guideline development and reports by similar groups such as GRADE have encouraged the incorporation of the patient perspective in the guideline development process; adding this perspective helps support the goal of patient-centered care.

Numerous organizations have stressed the need to reduce the susceptibility of guideline development groups to conflicts of interest and have established detailed procedures for assessing and managing both financial and non-financial conflicts (IOM, 2011a; USPSTF, 2018; WHO, 2015). Once potential group members have been identified, any conflicts of interest they have may be posted publicly to enhance transparency. One publicly available tool for identifying financial conflicts of interest is the Centers for Medicaid & Medicare Services' Open Payments national disclosure program, which publicly lists the financial relationships between applicable manufacturers and group purchasing organizations and physicians or teaching hospitals; however, other health care providers may not be included in Open Payments. The committee notes that although it is desirable to have experts from particular fields on CPG development groups, the very nature of their expertise may result in them having conflicts of interest that need to be disclosed.

DETERMINING THE SCOPE OF THE GUIDELINE

The first goal of the CPG development group is to determine the scope of the guideline, including the specific indications to be covered, as well as the populations, interventions, outcomes, and settings

to be addressed. The 2011 IOM report *Clinical Practice Guidelines We Can Trust* recommends that guideline groups consider

> a variety of clinical issues, including benefits and harms of different treatment options; identification of risk factors for conditions; diagnostic criteria for conditions; prognostic factors with and without treatment; resources associated with different diagnostic or treatment options; the potential presence of comorbid conditions; and patient experiences with health care interventions. (IOM, 2011, p. 98)

CPGs typically focus on clinical studies, which may be informed by basic research on opioids, including animal models. In the absence of clinical studies, basic research studies might be used to inform recommendations but these would be considered to be weak evidence.

USPSTF CPGs provide recommendations on clinical prevention activities such as screening for disease. The USPSTF procedure manual (2015) provides information on how to prioritize issues to be addressed in the CPG, how to frame key questions, and which outcomes to include. The manual states that its

> goal for topic selection and prioritization is to provide accurate and relevant recommendations that are as up to date as possible and to balance the overall portfolio of recommendations by population, type of service (e.g., screening, counseling, preventive medication), type of disease (e.g., cancer, endocrine disease), and size of project (e.g., update vs. new topic). (USPSTF, 2018)

AHRQ has a similar approach for prioritizing topics for comparative-effectiveness systematic reviews that includes clear and consistent criteria for prioritizing program activities and emphasizes the need to engage stakeholders in the process (Totten et al., 2019).

The goal of CPGs is to inform clinical practice and policy. However, recent experience indicates that some CPGs may be applied to situations for which they were not developed, with potential unintended consequences. For example, the 2016 Centers for Disease Control and Prevention CPG for chronic pain was used by many health care providers, insurers, and state regulators to limit prescribing for populations not intended for inclusion in the guideline, such as those who were opioid tolerant or who were currently prescribed higher doses than recommended. The harms of such misinterpretation have been discussed (Dowell et al., 2019; Kroenke et al., 2019). It is critical that CPGs clearly describe their scope as well as the clinical recommendations to help avoid such situations. Engaging a variety of stakeholders (including patients, payers, and policy makers) in the CPG guideline development process might help reduce unintended applications.

To delineate what surgical or medical indications the guidelines cover, a statement of scope and setting for the CPG is needed (e.g., policy, settings, patient populations, practitioner types). Such a statement is based on a clear description of the patient, problem, or population (P); intervention (I); comparison, control, or comparator (C); outcome (O); time (T); and setting (S)—the PICOTS framework (Schardt et al., 2007; University of Canberra, 2019). The scope of the CPG will be largely based on the PICOTS addressed in the key questions and supported by the systematic literature reviews. The PICOTS framework is used to identify the relevant literature and inform the evidence evaluation process. Health equity issues for various populations and indications may also be considered in the statement of scope (Welch et al., 2017).

Transparent and rigorous methods for guideline development will help optimize their acceptance and application. Together the key questions (discussed in the next section) and the PICOTS framework define the scope of the guideline, inform the analytic framework, and set the stage for the application of the evidence evaluation framework.

ANALYTIC FRAMEWORK

The analytic framework in Figure 4-2 identifies the evidence linkages to be evaluated in a systematic review of the effects of an intervention on health outcomes. The purpose of the analytic framework is to visually depict the evidence that CPG developers need to assess in order to make recommendations on opioid prescribing by indicating the populations addressed, treatment decisions, key health outcomes (rightmost box), the intermediate health outcomes associated with those health outcomes, the linkages between intermediate and health outcomes, and harms.

This framework, while specific to opioids, might be applied to other treatments for pain, including nonpharmacologic ones. It is based on the principle that interventions should improve overall health outcomes, not just intermediate outcomes, and that evaluations of interventions should be based on an assessment of benefits as well as harms. Defining the outcomes and showing the evidence linkages provides a structured framework by which CPG developers can assess the benefits and drawbacks of a given decision (in this case, different opioid prescribing strategies) (Harris et al., 2001; Woolf et al., 2012). The analytic framework enables guideline developers to articulate current evidence gaps and also potential obstacles to establishing the evidence base for assessing the outcomes of different opioid prescribing strategies.

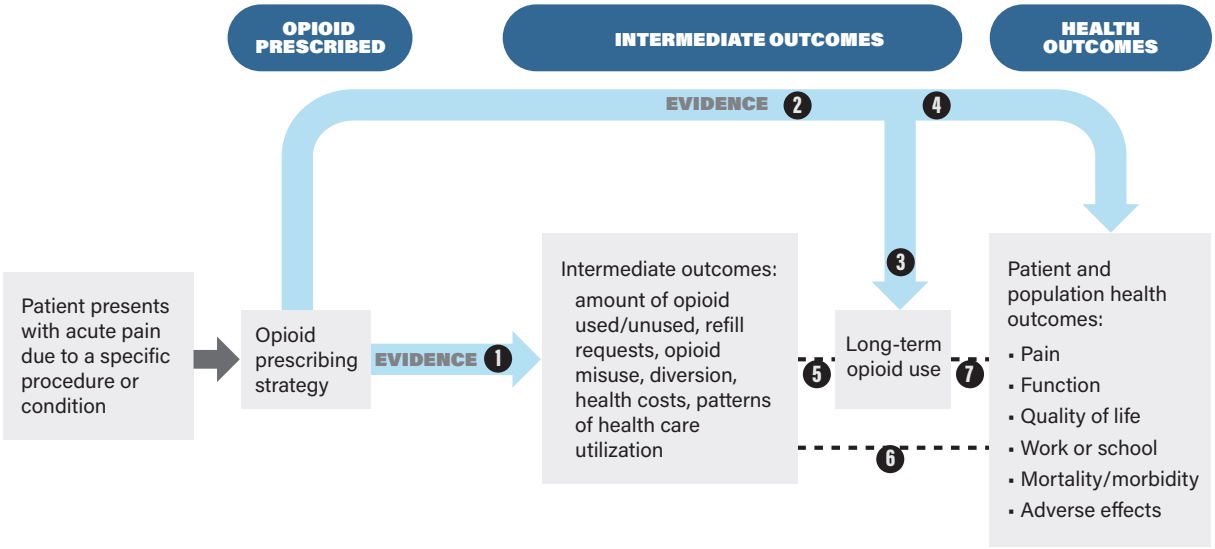

FIGURE 4-2 Analytic framework for prescribing opioids for acute pain. This figure shows the evidence linkages and key questions (see Box 4-1 for a list of questions that corresponds to the numbers in the circles) that are necessary to support the development of a CPG for opioid prescribing. The framework begins with an assessment of the patient who is presenting with acute pain and the demographic, social, genetic, and other factors that may affect the patient's presentation of pain (e.g., opioid-naïve patients versus opioid exposed) and response to treatment (described in Chapter 2). Opioid prescribing strategies may have direct evidence linking them to specific health outcomes or to intermediate outcomes or both. The wide arrows indicate evidence evaluating the effects of an intervention on a health or intermediate outcome. The dotted lines indicate linkages between different outcomes (e.g., the association between a lesser amount of opioid used and risk of long-term use or quality of life), not between an intervention and an outcome (or, in the case of intermediate outcomes and long-term opioid use, between one intermediate and another intermediate outcome). Short- and long-term health outcomes, both beneficial and harmful, may be at the patient and community or population levels.

Conceptual Rationale

The analytic framework presents a "roadmap" or chain of logic to guide the process of reviewing evidence to assess the outcomes associated with opioid prescribing for acute pain (Guirguis-Blake et al., 2007; Woolf et al., 2012). In general, analytic frameworks guide decision makers by showing how clinical treatment decisions (in the context of specific patient characteristics and needs) are linked to downstream outcomes of interest. Consistent with the committee's Statement of Task, the analytic framework is based on the assumption that opioids are appropriate for the management of the patient's acute pain and that the decision of interest is the optimal prescribing strategy. The analytic framework could be modified to incorporate effects of nonopioid therapies used either prior to or concurrently with opioids. The analytic framework indicates the key questions (typically using a PICOTS framework) (see Box 4-1) that will guide a literature review conducted to gather evidence to support the CPG.

The analytic framework clearly distinguishes intermediate outcomes from health outcomes (Wolff et al., 2018). *Health outcomes* are "symptoms, functional levels, and conditions that patients can feel or experience" (USPSTF, 2018), and they affect how long a patient lives or the quality of his or her life. For opioid prescribing for acute pain, important health outcomes include mortality, overdose, pain, function, adverse effects (e.g., psychological effects such as depression and anxiety), and quality of life. *Intermediate outcomes* for opioid prescribing strategies refer to outcomes that do not directly measure health outcomes, but rather measure events or endpoints that may be associated with health outcomes, such as the amount of opioid medication used versus the amount prescribed, the number of refill requests, misuse behaviors, health care use, or long-term opioid use. Both intermediate and health outcomes can be measured at short- or long-term follow-up and are important for the development of evidence-based CPGs.

BOX 4-1
Examples of Key Questions for Evaluating Effects of Opioid Prescribing Strategies for Acute Pain (see Figure 4-2)

1. In patients with acute pain requiring opioid therapy, what is the comparative effectiveness of different opioid prescribing strategies on intermediate outcomes (e.g., refill requests, unused pills, misuse, or diversion)?
2. In patients with acute pain requiring opioid therapy, what is the comparative effectiveness of different opioid prescribing strategies on health outcomes (e.g., pain, function, or quality of life)?
3. In patients with acute pain requiring opioid therapy, how do different opioid prescribing strategies affect long-term opioid use?
4. In patients with acute pain requiring opioid therapy, what effect do different opioid prescribing strategies have on the risk of harmful health outcomes (e.g., overdose, addiction, constipation)?
5. In patients with acute pain, what is the association between decreased opioid use and long-term opioid use?
6. In patients with acute pain, what is the association between decreased opioid use and health outcomes?
7. In patients with acute pain, what is the association between decreased long-term opioid use and health outcomes?

Proposed Linkages

The analytic framework in Figure 4-2 links the opioid prescribing strategies to intermediate outcomes (e.g., the amount of opioid used, refill requests, long-term opioid use) and to health outcomes (e.g., pain, functional status, mortality, and opioid-related adverse effects). As noted earlier, the analytic framework begins with the assumption that opioids will be used to treat the patient's acute pain. In the analytic framework, health outcomes may be linked directly to the opioid prescribing strategy (e.g., by studies comparing effects of different opioid prescribing strategies on pain, quality of life, or risk of opioid use disorder). When such evidence is limited or not available, the analytic framework also shows how the effects of an opioid prescribing strategy on health outcomes can be assessed indirectly via a chain of evidence involving intermediate outcomes. Intermediate outcomes may be useful for assessing the effects of opioid prescribing strategies when data on health outcomes are lacking and when the intermediate outcomes (e.g., number of unused opioid pills) are reliable proxies for health outcomes (e.g., accidental overdose) (Deschamps et al., 2019; Wolff et al., 2018). When there is sufficient direct evidence to evaluate the effects of an opioid prescribing strategy on health outcomes, it is not necessary to evaluate the effects on intermediate outcomes. Ultimately, the goal of the analytic framework is to link an opioid prescribing strategy with health outcomes so that the best prescribing strategy can be chosen on the basis of having the best health outcomes while minimizing opioid-related harms.

Patient Populations

The patient populations to be studied for a given prescribing strategy are defined during the scoping process described earlier. The prescribing strategies to be evaluated in the analytic framework may be based on the characteristics of the patient population in the study. These characteristics include the indication for pain (e.g., underlying medical condition or surgical procedure), demographic factors (e.g., age, sex, race/ethnicity), clinical factors (e.g., the presence of chronic pain, prior opioid use, the use of other medications or therapies, substance use history, psychiatric comorbidities, medical comorbidities), and practice setting (e.g., primary care, inpatient, ED). For example, the patient population to be studied for opioid prescribing, such as patients with a particular indication (e.g., low back pain), children, or patients who have substance use disorder, could be defined in the scoping process and evaluated with the analytic framework. Many of the studies cited in Chapters 2 and 6 explicitly state whether the study populations are opioid naïve, have prior opioid use, or have conditions that may affect their use of opioids for acute pain (e.g., Badreldin et al., 2018a; Bicket et al., 2019; Mudumbai et al., 2019). These patient factors are likely to be important for understanding the effects of opioid prescribing strategies and will help in individualizing such strategies; ideally they would be addressed in the analytic framework and subsequent CPG.

The effects of potential modifying factors within a population (e.g., children) can be evaluated through subgroup analysis after, for example, stratifying by age (e.g., children less than 5 years of age or older than 12 years of age). Other modifying factors that may need to be considered include sex, age, concurrent health concerns, and the use of prescription or over-the-counter therapeutics. Prescribing strategies may be assessed for a combination of pain conditions as well as for specific indications. Patient risk factors also need to be considered, such as whether patients are opioid naïve or have pre-existing opioid use or whether they have underlying mental health issues that may be exacerbated by opioids. Relevant modifying and risk factors should be articulated in the key questions and presented when describing the patient population to be studied and the study results. Explicit and well-defined study populations, including comparison groups when appropriate, are important for ensuring that the subsequent studies provide the necessary evidence to determine the effectiveness of a prescribing strategy.

Opioid Prescribing Strategies

The prescribing strategies indicated in the analytic framework are generally taken to mean that different opioid prescribing strategies are being compared across comparable populations with the same acute pain diagnosis (e.g., low back pain). For example, opioid prescribing strategies may refer to variations in the amount (dose or duration or both) of opioids that are prescribed (e.g., opioids for 3 days or 7 days or a dose of 20 morphine milligram equivalents [MMEs] versus 40 MMEs) for a particular indication (e.g., low back pain) or population (e.g., pediatric or geriatric patients); thus the effectiveness of one prescribing strategy may be compared with the effectiveness of another prescribing strategy (Daniels et al., 2011; Friedman et al., 2015; Kumar et al., 2017; Pathan et al., 2018). Converting opioid doses to MMEs allows for evaluation of opioid prescribing strategies that involve different opioids and formulations; the method or tables used to make the conversions should be indicated. For example, if hydrocodone, tramadol, and oxycodone are all reported MMEs, evaluating their effects may be facilitated. MMEs may not be the only factor informing or defining prescribing strategies—the route of administration or the specific opioid could also affect outcomes. CPGs should be clear about whether they address the route of administration or the use of a specific opioid.

Most assessments of opioid prescribing strategies have focused on effects of the amount of opioids prescribed, the number of unused opioid pills, and refill rates. However, some studies have evaluated effects of opioid prescribing strategies on health outcomes. For example, the Mayo Clinic in Minnesota evaluated opioid prescribing across 25 elective surgical procedures to determine what prescribing strategies were effective in reducing patient postoperative pain with the least number of leftover pills (Thiels et al., 2018). The survey results indicated that although the majority of patients were satisfied with their postoperative pain control regardless of the procedures performed, about 9% of the patients reported that their pain was not controlled with their discharge prescription of opioids.

A number of prescribing strategies have been developed based on patient-reported data on actual opioid use. For example, at the Dartmouth-Hitchcock Medical Center prescribing guidelines have been developed based on an internal assessment of postoperative prescribing practices for five inpatient surgeries and patients reports of pain management after discharge. Researchers found that the amount of opioids taken the day before discharge was highly correlated with the amount used after discharge (Hill et al., 2018). The Mayo Clinic (Thiels et al., 2018) and the Michigan Opioid Prescribing Engagement Network guidelines (PDOAC, 2018) are based on institutional assessments of the amount of opioids prescribed postoperatively versus the amount of opioids actually used by the patients for a variety of surgical procedures. Building on the concept of developing an opioid prescribing strategy that reduces the gaps between the amount of opioids prescribed and the amount used, some researchers and health care systems have begun attempting to "right size" opioid prescriptions by changing electronic health record (EHR) prescribing defaults, with some reports of success (Delgado et al., 2018). Although many of these studies do examine some short-term outcomes, including patient-reported pain, satisfaction, and the need for refills, they generally support the development of an opioid prescribing strategy and do not evaluate an already implemented strategy in terms of broader health outcomes.

The examples of the Mayo Clinic and Dartmouth-Hitchcock Medical Center guidelines highlight how to determine what opioid dosing strategies to evaluate, and are based on correlations and actual opioid use, but they do not compare one prescribing strategy with another. The analytic framework however, would compare the Dartmouth or Mayo approach with usual care or another prescribing strategy to determine if either the Dartmouth or Mayo approach actually reduces the amount of opioids used to achieve similar pain relief or other health outcome.

Intermediate Outcomes

Intermediate outcomes for opioid prescribing strategies at both the patient and the health care system level may include such markers as the amount of opioids used or unused, refill requests, and other measures of opioid use. The amount of opioids used by an individual may be a marker for long-term use and is associated with adverse health outcomes such as overdose (Babu et al., 2019; Deyo et al., 2017; Liang and Turner, 2015). Other intermediate outcomes that may be assessed include the development of tolerance, dependence, and withdrawal for both individuals and populations. The committee notes that these outcomes may be difficult to measure and may be highly variable among individuals. Limiting the number of MMEs, pills, or days of opioids to a level that is sufficient for the vast majority but not all patients with a specific condition means that some patients will have inadequate pain control with the amount prescribed. In lieu of evidence directly measuring the effects of an opioid prescribing strategy on pain, the number of refills requested and filled may be markers of inadequate pain control, a key outcome when applying these strategies to patients without ready access to refills. Conversely, basing opioid prescribing recommendations on patients with higher opioid requirements could mean more excess pills for the majority of patients. It is important that CPGs be transparent about how the trade-off between decreased opioid use and inadequate pain relief is evaluated.

Intermediate outcomes can be measured at short- or long-term periods after the intervention. Long-term opioid use, an intermediate outcome, does not directly measure effects on patient morbidity, mortality, or other health outcomes, but it may be a stronger marker for long-term adverse health consequences such as opioid use disorder and overdose than measures of short-term opioid use (Bohnert et al., 2011). Some studies on acute prescribing have assessed the long-term use of opioids (Brat et al., 2018; Brummett et al., 2017; Schroeder et al., 2019; Shah et al., 2017).

Intermediate outcomes can be assessed at the individual patient or health care system level, both of which may be useful for evaluating opioid prescribing strategies and clinical prescribing recommendations. For example, opioid use can be measured at the individual, health care system, or state levels. Assessing the diversion of unused pills from the prescription recipient to others and the misuse of opioids by the prescription recipient (e.g., use of the opioids for other purposes, such as a sleep aid) may also be predictive of opioid use disorder and its associated outcomes, such as overdose (Han et al., 2017).

Health Outcomes

The ultimate goal of an opioid prescribing strategy should be improved health outcomes and reduced opioid-related harms. A comprehensive assessment of health outcomes takes into account short- and long-term outcomes for the individual patient with acute pain and also for the community or population to which the patient belongs. Box 4-2 lists some of the short- and long-term health outcomes associated

BOX 4-2
Short- and Long-Term Patient and Population Health Outcomes Associated with the Use of Opioids for Acute Pain

- Pain relief
- Reduced use of opioids
- Improved quality of life
- Improved social and physical function
- Return to work or school
- Chronic pain
- Adverse effects
- Increased mortality and morbidity
- Increased substance use disorder or opioid use disorder

with the use of opioids for acute pain (Ferreira et al., 2002). Specific outcomes may be more important for some patients and communities than others. For example, patients may be willing to tolerate a certain level of pain if they are able to resume a favorite activity, whereas a community may be concerned with an increase in opioid overdose deaths rather than concerned about all individuals returning to work. When reviewing the evidence to identify an opioid prescribing strategy, the CPG developers should consider all relevant health outcomes, including adverse effects that may occur following opioid use, which may include but are not limited to constipation, nausea, sedation, respiratory depression, and hyperalgesia (Benyamin et al., 2008). Opioids have also been associated with disrupted sleep patterns in both current and past users (Gordon, 2019). Increased mortality and morbidity may include substance use disorder, opioid overdoses, and deaths from overdoses. For some patients, outcomes such as improved function, return to work, or the ability to breastfeed an infant may be more important goals than the elimination of pain. The health outcomes to be considered by the CPG developers should be determined in the scoping step described earlier. Thus, it is important that CPGs are transparent about the methods they use to prioritize outcomes.

Large-scale studies that evaluate outcomes in large populations on a community or population level, or both, would help address important unanswered questions such as (1) Does the reduced potential for opioid diversion result in fewer people who start to misuse prescription opioids? versus (2) Does the reduced potential for opioid diversion result in a higher conversion rate of prescription opioid users and misusers to nonprescription opioid users? (NASEM, 2017).

LITERATURE SEARCH AND RETRIEVAL

The analytic framework identifies the links where evidence needs to be gathered and reviewed on opioid prescribing strategies. Gathering that evidence requires that a comprehensive and well-structured literature search be conducted on the basis of the PICOTS framework developed during the earlier scoping step.

Many organizations have established standard methods for searching the literature, such as the 2011 IOM report *Finding What Works in Health Care* (IOM, 2011b), the 2018 USPSTF *Procedure Manual*, the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2019), and the 2015 AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (AHRQ, 2015). Each of these documents discusses the need to have qualified information specialists conduct the searches using relevant terms that have been discussed with the guideline developers who will be using the results (Shekelle et al., 1999).

EVIDENCE EVALUATION FRAMEWORK

The evidence evaluation framework outlines a process by which CPG developers may assess the evidence indicated by the linkages in Figure 4-2. Such evaluations can then be used to determine the strength of recommendations for an effective opioid prescribing strategy.

Conceptual Approach

The primary concept in the evidence evaluation framework is that the most effective and trustworthy guidelines are based on the highest-quality evidence. Discussions of "quality" have often focused on issues related to the internal validity and risk of bias. However, as noted in the 2011 IOM report *Clinical Practice Guidelines We Can Trust*, the concept of quality can be broad, that is "the level of confidence

or certainty in a conclusion regarding the issue to which the evidence relates," with that confidence and certainty frequently expressed as numeric grades or scores of the evidence. The IOM report also noted that the quality of evidence can incorporate other considerations, such as those described by Verkerk et al. (2006, p. 110):

> the relevance of available evidence to a patient with particular characteristics; the quantity (i.e., volume and completeness) and consistency (i.e., conformity of findings across investigations) of available evidence; and the nature and estimated magnitude of particular impacts of an individual clinical practice and value judgments regarding the relative importance of those different impacts.

A key issue that arises in using the analytic framework shown in Figure 4-2 is that while ideally there would be a strong evidence base linking each opioid prescribing strategy to a health outcomes, in practice such studies, particularly randomized controlled trials (RCTs) may not be available and can be difficult to conduct, particularly for longer-term outcomes. Thus, the preponderance of evidence will most likely be derived from observational studies, which are useful, but more susceptible to bias and confounding. Therefore, the quality of the overall evidence base for the effectiveness of any specific opioid prescribing strategy is likely to be low. Assessing the effects of opioid prescribing strategies on health outcomes may be difficult, particularly for longer-term and population-level outcomes. Assessing how these strategies affect intermediate outcomes, such as the amount of opioid prescribed or used, may be easier and, indeed, many studies have done so (Hill et al., 2018; Larach et al., 2018; Lee et al., 2019). These studies, in the absence of higher-level evidence, may best inform recommendations to reduce excess prescribing and minimize the flow of unused opioids available for diversion to unintended users until better evidence is available.

For many indications, the committee expects that there will be little evidence linking a prescribing strategy to health outcomes, so that indirect evidence on intermediate outcomes will need to be used for the development of CPGs. Evidence can be used to establish the linkages between opioid prescribing strategies and health outcomes via intermediate outcomes.

Types of Evidence

CPGs consider various types of evidence in order to assess the linkages between specific opioid prescribing strategies and intermediate health outcomes in patients with acute pain (White and Schmidler, 2018) (see Figure 4-2). RCTs, observational studies, and quality improvement initiatives may provide evidence for the linkages in the analytic framework, usually evaluated by conducting a systematic review. Each of these types of evidence is discussed below. Although expert opinions are sometimes cited as evidence in CPGs, when they are included they are considered the weakest form of evidence (Canadian Task Force on the Periodic Health Examination, 1988; Centre for Evidence-Based Medicine, 2009). Furthermore, the use of the term "expert opinion" is subject to various interpretations depending on the CPG development process. CPGs may need to rely on expert opinion when published evidence is lacking; if there are other reasons for using expert opinion for a CPG, they should be described.

All CPGs require a consensus process to make recommendations, although the specific process used can vary from informal, ad hoc methods to formal consensus methods such as Delphi. An analysis of 69 published guidelines using expert consensus as a means to formulate recommendations found that a rationale for using this method was lacking in 91% of the recommendations. Therefore, when expert consensus is used to develop a CPG, it is important that the developers define what expert consensus means and describe the methods by which it was reached (Ponce et al., 2017).

Randomized Controlled Trials

RCTs, the gold standard for assessing clinical interventions, compare the effect of an intervention with a control (either another intervention or a placebo). The main advantages of RCTs are that, if conducted well, they are the study design most able to minimize or reduce the risk of bias when assessing the effects of interventions. Importantly, the randomization of patients to intervention or control groups removes allocation bias, with the two groups having an unbiased and equal distribution of potential confounders, assuming an adequate sample size (Süt, 2014). The disadvantages of RCTs are that they are typically expensive and time-consuming to perform and that they are often designed in ways that limit the applicability of the findings to clinical practice (Corrigan-Curay et al., 2018). For example, an RCT may enroll only populations that are at low risk of harm (e.g., excluding patients with prior substance use disorders or psychiatric disorders), or it may evaluate an intervention such as a method to enhance adherence that is not feasible in clinical practice (e.g., having a nurse follow-up with a patient on a daily basis).

Of concern for this report is that few RCTs comparing health outcomes of different opioid prescribing strategies have been conducted and published. Given the extensive resource demands of conducting RCTs, they may most easily be designed to evaluate immediate outcomes (e.g., opioid use) or short-term health outcomes (e.g., a reduction in acute pain or improvements in patient function) rather than long-term or uncommon outcomes. For example, it is challenging to conduct RCTs to assess harmful outcomes such as opioid overdose, the development of opioid use disorder, or the development or persistence of chronic pain and reduced quality of life. Other limitations for RCTs include restrictive eligibility criteria, resulting in populations that are easier to evaluate and more likely to respond to a given treatment, and a loss of study participants over time.

The committee recognizes the challenges in carrying out long-term RCTs to assess the effects of opioid prescribing strategies on such outcomes as overdose and opioid use disorder at the individual or population level. One of the major challenges of conducting this type of study is accurately ascertaining the adverse events. For example, overdoses may be mis- or underreported, may occur outside the study venue (e.g., at a different health care facility), or, in the case of death, may not be reported to the researchers at all. The committee notes that new technologies such as machine learning, particularly the use of logic and algorithms, may improve patient selection, provide predictive long-term outcomes, reduce the time and cost of clinical trials, and improve researchers' ability to process large datasets (Rademacher, 2019). RCTs may also need to control for factors such as the variability in health insurance for the study population or changes to opioid prescribing policies at the individual prescriber, institution, insurer, or state levels.

Observational Studies

In observational studies, researchers make no attempt to affect the outcome of an intervention in a population (NCI, 2019), nor do the researchers control how subjects are assigned to groups or which intervention each group receives (Stat Trek, 2019). Observational studies may be descriptive (e.g., case-report, case series) or analytic (e.g., prospective and retrospective cohort studies, case-control studies, and cross-sectional studies) (Süt, 2014). Data sources include administrative databases, clinical registries, EHRs, and directly querying patients via surveys or interviews. However, all of these data sources have potential problems, such as the accurate measurement of interventions and the determination of both intermediate and health outcomes. Nevertheless, there are methods that researchers may use to reduce the variability in the data. For example, observational studies based on insurance claims data will typically not provide direct information on pill use, but pill use may be inferred by the timing of refill requests or

by querying patients. The committee notes that observational studies based on administrative or EHR data may not capture patient-centered outcomes such as return to work or improved mobility. Therefore, these studies may need to combine administrative data with data on patient-reported outcomes—for example, unused pills, pain control, and functional status—gathered using methods such as patient surveys to provide a more complete picture of the outcomes of opioid prescribing. Retrospective studies that query patients about past exposures may be subject to recall bias, particularly when the patient is asked to recall information several months in the past; although, there are techniques that may be used to reduce this bias such as timeline follow back.

Observational studies have several potential advantages over RCTs. While RCTs often enroll a relatively small number of selected participants who meet eligibility criteria, populations in observational studies may better reflect the broader range of patients seen in clinical practice. Observational studies are generally more efficient and require fewer resources, enabling evaluation of larger samples of participants and longer follow-up for outcomes, including patient-centered outcomes such as improved quality of life. The main drawback to observational studies is that they are more susceptible to bias and confounding than well-conducted RCTs. As with RCTs, an observational study may also have poor generalizability or applicability to nonstudy populations if appropriate consideration is not given to how the study populations are defined and obtained, what interventions are to be assessed, what outcomes are evaluated, and what comparisons are to be made. Short-term efficacy outcomes and opioid use outcomes may be more reliably—though not exclusively—assessed in RCTs because they are less susceptible to bias and other issues associated with observational studies (Anglemyer et al., 2014; Hannan, 2008).

The link between intermediate outcomes and health outcomes has to be evaluated by observational studies, as it is not possible to randomize patients to an intermediate outcome. The limitations of observational studies for supporting such linkages also need to be recognized. A major limitation is that the observed association between intermediate and health outcomes can be the result of measured and unmeasured confounding variables. It is critical that such studies control for potential confounders (e.g., age, sex, pain severity, and comorbidities). Other limitations of observational studies may include temporal confounders, changes in the use of other interventions such as opioid-sparing approaches, differences in case mix and selection bias, measurement bias with respect to assessing pain, and opioid-related outcomes.

Quality Improvement Initiatives

Quality improvement initiatives examine the implementation of interventions designed to enhance the quality of clinical care and encourage the uptake of best practices. These initiatives are focused on pragmatic changes intended to address a specific clinical problem, and they typically take advantage of nonrandomized designs examining the effect of a health intervention by examining specific outcomes prior to and after implementation (Chassin and Loeb, 2011). Quality improvement initiatives may be designed specifically to affect local environments, such as institutions or health care systems, and often integrate immediate feedback in order to refine the interventions and optimize their implementation. However, quality improvement initiatives may not explicitly address hypothesis testing, may not assess and minimize bias, and may not provide findings that are generalizable to other populations (Itri et al., 2017). Although each of these components (hypothesis testing, bias evaluation, generalizing findings) may be considered in these studies, they are secondary priorities. Quality improvement initiatives may also commonly involve the creation of targets for best practices, performance assessment, feedback to key stakeholders, and education about and dissemination of interventions.

Quality improvement initiatives may be advantageous in that they allow for the rapid assessment of potential interventions in order to address urgent or important clinical problems, particularly those in which more rigorous designs may be costly, logistically difficult, or ethically challenging (Neuhauser and Diaz, 2007). For example, it may not be feasible to randomize or blind participants to an intervention, or it may be challenging to accrue a sufficiently homogeneous sample in a study with numerous exclusion criteria. In this context, quality improvement initiative designs may lack sufficient rigor to assess causality, and issues with confounding, mediating, and moderating effects may cloud findings. Quality improvement initiatives often leverage a number of different study design types, including qualitative assessment and quasi-experimental approaches, including uncontrolled and controlled pre/post intervention testing using time-series and difference-in-difference analysis techniques.

Criteria for Evaluating the Evidence

Once the literature has been systematically searched and relevant studies have been identified, the next step in the CPG development process is to carry out a critical evaluation of the evidence base for each of the linkages specified in the analytic framework. Several organizations, including GRADE, ARHQ, and Cochrane, have developed formal methods to evaluate the evidence base for clinical questions in systematic reviews. These approaches typically assess the strength of the evidence on the basis of (1) the quantity of evidence (e.g., number of studies) and (2) the quality of evidence (e.g., the type of studies and how well the studies were performed). A brief description of the GRADE approach is given below; ARHQ uses the GRADE principles to review evidence. Cochrane is focused on producing systematic reviews only and is not included here; an in-depth description of the Cochrane methodology may be found online. Other approaches to conducting systematic reviews may be found in the 2011 IOM report *Finding What Works in Health Care*.

Grading of Recommendations Assessment, Development and Evaluation

GRADE is a standardized and systematic approach to grading the quality of evidence (indicating certainty in findings) and the strength of recommendations based on that evidence. GRADE has been adopted by many health care organizations for evaluating evidence and developing CPGs. The GRADE system classifies the quality of evidence into four levels (Schünemann et al., 2013):

- High: Very confident that the true effect lies close to that of the estimate of the effect;
- Moderate: Moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- Low: Confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; and
- Very low: Very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

These classification levels are applied to the body of evidence rather than to individual studies (Balshem et al., 2011). RCTs begin as high-quality evidence but may be rated lower if there are study limitations, inconsistency of results, indirectness of evidence, imprecision, or reporting bias. Observational studies on the other hand, begin with a low quality rating but may be rated upward if the magnitude of the treatment effect is very large, if there is evidence of a dose–response relationship, or if all plausible

biases would decrease the magnitude of an apparent treatment effect (Guyatt et al., 2008a,b). GRADE rates the quality of the body of evidence using the following criteria (Zhang et al., 2019):

- Study limitations
- Publication bias
- Imprecision (random error)
- Inconsistency
- Indirectness
- Rating up the quality of evidence
- Resource use

In the GRADE approach, study limitations that decrease confidence in the findings include a lack of allocation concealment; a lack of blinding; incomplete accounting of patients and outcome events; selective outcome reporting bias; stopping early for benefit; the use of invalidated outcome measures (e.g., patient-reported outcomes); carryover effects in crossover trials; and recruitment bias in cluster-randomized trials (Guyatt et al., 2011).

FROM EVIDENCE TO RECOMMENDATIONS

The goal of the prior steps in the CPG development process (see Figure 4-1) is to identify, gather, review, and grade the evidence on which CPG developers can make recommendations regarding appropriate prescribing strategies to achieve the best health outcomes for the patient and community and to minimize any harms associated with those strategies. The strength of the evidence gathered in the prior step provides the basis for any CPG recommendations.

One approach for moving from the strength of the evidence to recommendations is the methodology developed by GRADE. This methodology addresses factors such as the magnitude of benefits relative to harms, costs, values and preferences, feasibility and implementability, and equity issues, among others (Schünemann et al., 2008). CPG developers can evaluate the evidence for each of the linkages in the analytic framework using the GRADE criteria and evaluate whether a prescribing strategy is associated with benefits (e.g., decreased overdoses) that outweigh harms (e.g., a slight increase in average pain). Assessing the balance of benefits to harms requires a consideration of how health outcomes have been prioritized by the CPG development group during the scoping step. For example, the development group may decide that reducing opioid overdoses and opioid use disorder is a more important health outcome than patients experiencing slight increases in pain. Weighing the findings accordingly, the CPG developers then determine whether to recommend a particular prescribing strategy.

The GRADE methodology determines recommendation strength (strong, weak, or conditional) based on the certainty and balance of an intervention's desirable effects versus its undesirable effects (Guyatt et al., 2008a). Using the GRADE criteria, strong recommendations are more likely when the following conditions are met:

- The strength of the evidence has been rated as high;
- There is a large benefit from the prescribing strategy relative to potential harms;
- There are lower costs associated with one prescribing strategy compared with another for either the patient or the health system or both;
- It is feasible to implement the strategy;
- The strategy will improve health equity (e.g., better access to care); and
- The strategy is acceptable to patients and their health care providers.

If the evidence does not support the linkages from a prescribing strategy to improved health outcomes (directly or indirectly) then the CPG developers may opt either to not make a recommendation or to make a recommendation but be very explicit about the low quality of the supporting evidence. Often patients and clinicians will accept strong recommendations, whereas the acceptance of weak recommendations will vary according to patients' and clinicians' values and preferences. Therefore, when the evidence is low quality but there is little risk of harm and a high likelihood of benefit, a strong recommendation could be formulated based on weak evidence. The GRADE Working Group has identified five specific contexts for such recommendations, three of which are relevant to opioid prescribing (Andrews et al., 2013):

- Low-quality evidence suggests benefit in a life-threatening situation (evidence regarding harms can be low or high).
- High-quality evidence suggests equivalence of two alternatives, and low-quality evidence suggests harm in one alternative.
- High-quality evidence suggests modest benefits, and low- or very low-quality evidence suggests the possibility of catastrophic harm.

The committee notes that for opioid prescribing for acute pain, CPGs are being developed in the context of well-established harms associated with long-term opioid prescribing at the individual patient, community, or population levels and of evidence linking acute prescribing with long-term use. Therefore, opioid prescribing recommendations that have the potential to reduce such harms by decreasing unnecessary opioid use for acute pain may be reasonable even if the evidence showing effects on improved health outcomes is weak. Recommendations supported by low-quality evidence require a clearly articulated rationale, particularly for strong recommendations, and should clearly describe the evidence gaps needed to improve the quality of evidence.

CPG recommendations to clinicians and policy makers will be more acceptable if they are practical, with a focus on relieving patients' acute pain while minimizing the untoward risks of opioids. Indeed, the risk profile of opioids may justify recommendations to change opioid prescribing patterns based on relatively lower levels of evidence (Ross et al., 2017). Moreover, the potential serious harms that may result from inappropriate opioids prescribing (e.g., misuse, diversion) are challenging to study with RCTs and even observational studies, and may further justify strong recommendations based on weak evidence, if they are determined to have the potential to substantially mitigate such harms (Schünemann et al., 2013; Stancliff et al., 2015).

IMPLEMENTATION

CPG implementation addresses how CPGs relate to different clinical practices and clinical settings, how to increase the dissemination, applicability, and impact of guidelines, and how to evaluate the impact of the guideline on health outcomes. A critical requirement of CPG implementation is continuous quality improvement, including practice audits and feedback (Dulko et al., 2010; Grimshaw et al., 2012; Hysong et al., 2006). As each CPG is disseminated and applied in practice, outcome data need to be gathered at the individual and community levels. Such information can assist guideline developers in revising and updating the CPG when necessary so that it reflects the most current evidence available to ensure that patients with acute pain receive the best care.

Although evidence suggests that CPGs may reduce hospitalization rates, reduce health care costs, and improve clinical outcomes, barriers often exist that limit providers from adopting and implementing them (Kroenke et al., 2019). Guidelines that are overly complex or require a significant change in

practice or resources are less likely to be implemented. An organizational structure that allows for access to high-quality CPGs, strategies for decision making, and collecting outcome data may help overcome challenges to the implementation of guidelines.

After recommendations for opioid prescribing strategies have been developed and approved, consideration needs to be given to ensuring effective dissemination, uptake, and periodic revisions of the CPG. As discussed in the 2011 IOM report *Clinical Practice Guidelines We Can Trust*, these activities are part of the implementation process. Many organizations that develop CPGs already have mechanisms in place to disseminate them to appropriate audiences. For example, members of medical specialty societies may learn about a new CPG or changes to an existing CPG through annual or regional meetings, continuing medical education activities, or educational materials from state medical boards. Other dissemination activities may also be used to encourage clinician knowledge of CPGs. Meisel et al. (2016) found that ED physicians who read narrative vignettes that referenced opioid prescription dilemmas published in the daily electronic newsletter of the American College of Emergency Physicians were significantly more likely to read additional information in the newsletter links than were physicians who accessed newsletters that contained traditional summary text.

Some CPGs include recommendations on implementation and how they might best be incorporated into clinical practice. Implementation of opioid prescribing strategies may include components such as EHR standing orders, provider education, and pharmacy reviews. For example, a recent CPG for acute pain management after musculoskeletal injury includes best practice recommendations for health care systems that include supporting opioid education efforts for prescribers and patients and the use of clinical decision support for opioid prescribing in the EHR (Hsu et al., 2019). That CPGs are not necessarily used for clinical decision making was demonstrated by Kilaru et al. (2014), who found that among 61 ED physicians, hospital-based guidelines were primarily used to communicate decisions to limit discharge prescriptions to patients rather than as decision-making tools. Overcoming this lack of clinician uptake may include both provider and patient education efforts. Kaafarani et al. (2019) found that a hospital-based, multidisciplinary pain management intervention to reduce postoperative opioid prescribing was effective in reducing both discharge prescribing as well as refill requests and sex and race prescription disparities. The intervention consisted of consensus-built opioid prescribing guidelines for 42 surgical procedures from 11 specialties, provider-focused posters displayed in all surgical units, patient opioid/pain brochures to set patient outcome expectations, and educational seminars to residents, advanced practice providers, and registered nurses.

Similarly, other CPG developers address strategies to enhance patient engagement, such as patient education and counseling, and to promote patient adherence to and acceptance of the clinical care protocols outlined in the CPG (Engelman et al., 2019). Patient education may include information on the risks and benefits of opioid use, including drug interactions, and what to do should adverse effects occur. Both clinicians and other trained health care providers (e.g., nurses, pharmacists, social workers) can educate patients on the appropriate use and disposal of opioids, and who to contact in the event of adverse effects.

Tools, checklists, applications, algorithms, and pocket guides have been successfully used to increase guideline uptake by clinicians (CDC, 2017). For example, one medical center found that mandatory prescriber training and standardized patient instruction materials along with the availability of evidence-based CPGs significantly reduced opioid prescribing for patients undergoing breast and melanoma surgical procedures (Lee et al., 2019).

States also have mechanisms to encourage clinicians to use opioid prescribing guidelines. Health care providers who are identified as high prescribers on the basis of state prescription drug monitoring programs (PDMPs) may be notified that they are exceeding the guidelines or regulatory limits, alerting

them to reconsider their prescribing patterns (e.g., the State of Illinois Opioid Action Plan, 2018). Moreover, PDMP data can be used to track the impact of these statewide programs on opioid prescribing practices (Deyo et al., 2018).

The use of CPGs in clinical care requires further study, but some reviews have suggested that "multifaceted educational knowledge translation interventions" are effective for improving the use of guidelines by health care professionals (Al Zoubi et al., 2018). The committee emphasizes that without practical approaches to implement guideline recommendations, the impact of evidence-based CPGs will be less than optimal. Such activities can be incorporated into a continuous quality improvement approach for implementation. Other factors that may affect how guidelines are implemented include urban versus rural setting, health care setting (e.g., large or small hospitals, single clinician clinics), the social determinants of health (e.g., access, bias, stress, marginalized groups), opportunity for continuity in patient care, the presence of a definitive diagnosis, and multiple clinicians (e.g., transitioning from surgeon-directed, postoperative pain control to primary care provider postoperative pain control) (Haller and Acosta, 2010; IOM, 2011a; Klueh et al., 2018; Meghani et al., 2012; Sadhasivam et al., 2012). For example, Hill et al. (2018) developed a guideline for opioid prescribing based on the number of opioids used by the patient the day before discharge. Hill et al. (2018) noted that the guideline had a benefit over state-mandated prescribing practices because prescribing was determined with the patient using a shared decision-making model (Osmundson et al., 2018).

Critical to the dissemination and uptake of CPGs is the integration of new and emerging technologies (e.g., telemedicine, e-prescribing, phone or email follow-up) to improve the implementation and monitoring of CPGs. EHRs may be a valuable resource for identifying overprescribing as well as identifying data sources that can be used to establish baseline or default prescribing doses or trends in opioid prescribing (Garcia et al., 2019; Suffoletto et al., 2018). Such records can be modified to capture specific intermediate and health outcomes and to document confounders that may be used in future observational studies. As EHRs are able to incorporate more discrete data, subsequent cohort research can incorporate such data to more accurately address potential confounding factors (e.g., health literacy). Such defaults may require the clinician to justify prescribing opioids in excess of the default amount.

As guidelines are implemented, the appropriate monitoring of patient and populations health outcomes is important to ensure that the changes in clinical practice as a result of the guideline are effective. This monitoring may include identifying such things as unresolved pain, lack of functional benefits, a continued need for opioids, conversion to chronic pain, opioid misuse, opioid diversion, and opioid-related adverse events including serious adverse events (e.g., fatal and nonfatal overdose, central nervous system depression, and respiratory depression).

Inherent in the development of a CPG is the need to periodically update and revise the CPG as new evidence becomes available through a defined process of periodic review and updating (orange arrow in Figure 4-1). This process might also include a need to revise either the CPG or the implementation process in light of both intended and unintended consequences or information that suggests the CPG is not effective in improving intermediate or health outcomes (Dowell et al., 2019; Kroenke et al., 2019). As stated in the 2011 IOM report:

> CPGs should be updated when new evidence suggests the need for modification of clinically important recommendations. For example, a CPG should be updated if new evidence shows that a recommended intervention causes previously unknown substantial harm; that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective; or that a recommendation can be applied to new populations. (p. 137)

Monitoring the effectiveness of a CPG for improving opioid prescribing practices may include encouraging, mandating, or expanding access to PDMPs and educating prescription benefits managers (Alexander et al., 2015). The committee cautions, however, that such monitoring may indicate that recommended strategies are having unintended effects. For example, in one case the mandated use of a PDMP did not the reduce the number of opioid pills prescribed to patients following surgery or the number of patients who received opioids in the 6 months after the program was initiated compared with rates prior to initiation of the program nor did the program identify at-risk patients who should not receive opioids (Stucke et al., 2018). Guidelines also create the possibility of unintended consequences, such as a health insurance company placing restrictions on opioid prescribing regardless of individual patients' needs (Dowell et al., 2019).

Therefore, CPGs should formalize a plan to track how they are being used in order to assess (1) the desired direct effects, (2) undesired direct effects (e.g., greater frequency of uncontrolled pain), (3) desired indirect effects, and (4) undesired indirect effects (e.g., increased use of illicit opioid substances). Guideline developers should consider addressing risk mitigation strategies (e.g., education, opioid disposal, monitoring) as part of developing a comprehensive care plan to address these concerns and to identify others (e.g., PDMPs, concurrent opioid therapy, concurrent benzodiazepine therapy, multiple prescribers or "doctor shopping").

As pain and opioid-related CPGs are published, it will be important to evaluate the methodological rigor of the guidelines using instruments such as AGREE II, to assess the consistency of recommendations, and to determine best practices to promote the uptake of CPGs. These evaluations will also be useful to help CPG developers align their work with other high-quality CPGs and address shortcomings of existing ones (Al Zoubi et al., 2018; Durán-Crane et al., 2019; Lee et al., 2014).

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5

Identifying and Prioritizing Indications for Clinical Practice Guidelines

In addition to developing a framework to evaluate existing clinical practice guidelines (CPGs) for opioid prescribing for acute pain, the National Academies of Sciences, Engineering, and Medicine (the National Academies) committee was tasked with identifying and prioritizing up to 50 specific surgical procedures and medical conditions that are associated with acute pain and for which opioid analgesics are commonly prescribed. The committee was also tasked with recommending where evidence-based CPGs would help inform prescribing practices. To accomplish this task, the committee considered the 1995 Institute of Medicine (IOM) report *Setting Priorities for Clinical Practice Guidelines*, which recommended that:

> six general criteria be applied in considering topics for either guidelines development or technology assessment. These criteria are prevalence of the clinical problem (number of affected persons per 1,000 persons in the general U.S. population); burden of illness imposed by the problem (individual mortality, morbidity, or functional impairment); cost (cost per person of managing the problem); variability in practice (significant differences in utilization rates for prevention, diagnosis, or treatment options); potential of a guideline or assessment to improve health outcomes (expected effect on health outcomes); and potential of a guideline or assessment to reduce costs (expected effect on costs to sponsoring organization, other relevant agencies, patients and families, and/or society generally). (p. 4)

The committee agreed that the criteria in the 1995 IOM report would help it identify surgical and medical indications for which evidence-based CPGs for opioid prescribing for acute pain should be developed. However, it also recognized that obtaining and reviewing such information on all possible surgical and medical indications associated with acute pain and for which opioids have been prescribed would not be feasible in the committee's timeframe. Ideally, evidence-based CPGs could be developed for all indications, but such a task might be prohibitive, given the rapid rate of change in treatment practices and the volume of information being generated on opioid prescribing and other acute pain interventions. For many indications, opioid prescribing practices continue to evolve as they integrate new evidence, such as the effectiveness of nonopioid pharmacotherapies for acute pain indications (e.g.,

acetaminophen and nonsteroidal anti-inflammatory drugs), the introduction of opioid-sparing or highly restrictive acute pain protocols, and the implementation of state and federal policies restricting opioid prescribing in response to rising opioid-related morbidity and mortality.

The committee's approach to identifying and reviewing the literature and other data sources to develop the priority list of indications is detailed in Chapter 1 in the section on the committee's approach. The committee's method for identifying guidelines for the surgical and medical indications is given below.

METHODS FOR IDENTIFYING PRIORITY SURGICAL AND MEDICAL INDICATIONS FOR CLINICAL PRACTICE GUIDELINE DEVELOPMENT

The committee used the key factors in Box 5-1 to prioritize the surgical procedures given in Table 5-2 and the medical conditions given in Table 5-3 to produce a list of candidates for the development of CPGs. The committee deemed these indications to have the greatest potential public health impact based on the frequency of the surgical procedure or prevalence of the medical condition, the variation in opioid prescribing practices, and the potential harms in light of various patient- or procedural-related factors, such as prescribing for vulnerable patients (e.g., children and patients with a history of or current opioid use disorder). The committee notes that it considered all of the indications in the two tables to be priorities and did not rank them (they are listed alphabetically); thus, one indication should not be considered of greater priority than another in either table.

After the list of priority indications had been developed on the basis of public health impact as described in Chapter 1, the committee determined whether some type of clinical guideline had been published for that indication. A literature search was conducted specifically to identify any guidelines published for the indications listed in Tables 5-2 and 5-3 (see Appendix B for the search strategy and the number of citations retrieved). The availability or lack of a guideline did not affect whether the indication was included in a table. Although the committee divided the list of indications into surgical conditions and medical conditions, it recognized the potential for overlap, as some medical conditions might ultimately require surgical or procedural interventions (e.g., nephrolithiasis), and some surgical indications may subsequently require medical management (e.g., cholecystectomy).

The committee also conducted a literature search to identify CPGs that were specific for (1) opioids, (2) acute pain, and (3) a specific indication (see Appendix B for the search strategy and the number of citations retrieved). Few guidelines met all three criteria, but numerous guidelines met at least two of the criteria. For example, several CPGs broadly address both acute and chronic pain, but are not specific for a particular surgical or medical indication. These include the American Society of Interventional Pain

BOX 5-1
Key Factors for the Prioritization of Indications for Clinical Practice Guideline Development

- Prevalence of the surgical procedure or medical indication;
- Variation in opioid prescribing across providers;
- Variation in opioid prescribing in relation to patient-centered or patient-reported outcomes; and
- Availability of an evidence-based CPG that describes opioid prescribing for acute pain associated with the indication.

Physicians (ASIPP) *Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain*, which includes an extensive evidence assessment (Manchikanti et al., 2012. Note: Page S83 of the guidelines says the principles may be "applied for patients who are treated for acute pain management, but also have other risk factors and for whom pain may become chronic"). ASIPP's development process for the guidelines was based on the recommendations in the 2011 IOM report *Clinical Practice Guidelines We Can Trust*. CPGs such as the *VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain* (VA/DoD, 2017) and the *CDC Guideline for Prescribing Opioids for Chronic Pain* (Dowell et al., 2016) also briefly address acute pain as well as chronic pain (see Chapter 3 for other examples of guidelines). Several evidence-based CPGs address acute pain following surgery but are not procedure specific, such as the Society for Pediatric Anesthesia's recommendations on the use of opioids in children during the perioperative period (Cravero et al., 2019). If an indication had an evidence-based CPG on opioid prescribing for acute pain that met the committee's analytic framework, it would not have been included in either Table 5-2 or Table 5-3; however, none of the CPGs or other guidelines reviewed by the committee for any of its selected indications did so.

Challenges to Creating an Algorithm for Prioritization

Because of the heterogeneity of the potential indications for acute pain, the committee did not create a standardized algorithm for prioritizing the creation of CPGs. For example, for some indications, such as carpal tunnel release, there is strong evidence of overprescribing, but the occurrence of these procedures is relatively infrequent compared with other procedures such as hernia repair (Steiner et al., 2017). Similarly, the committee deemed other indications, such as neck pain, to be of lesser priority for CPG development because of the heterogeneity in its presentation, cause, severity, and time course. As another example, although traumatic injuries are common, there is wide variety in the severity, treatment, and presence of other injuries that may make the creation of broad, overarching CPGs regarding opioid prescribing difficult. Finally, the availability of evidence was mixed for each prioritization factor across indications (e.g., the prevalence of the condition, the prevalence of opioid prescribing, variation in prescribing, and associated harms) and often not uniformly available, limiting the committee's ability to account for or compare each of the factors across conditions and precluding a weight-of-the-evidence approach to prioritization. Realizing that others might prioritize conditions differently, the committee has provided the evidence it used to reach its priorities in Tables 5-2 and 5-3.

The committee emphasizes that because of substantial variation in the presentation of acute pain, the list of priority indications developed by the committee in Tables 5-2 and 5-3 should not be considered to be as exclusive or exhaustive. There are other factors that may influence the inclusion of a condition for CPG development, including opioid prescribing practices, strong stakeholder advocacy, the probability of converting acute to chronic pain, and expert judgment.

SURGICAL INDICATIONS OVERVIEW

Surgical Care and Opioid Prescribing

In 2014 there were approximately 17 million hospital visits related to 22 million surgical procedures in the United States (Steiner et al., 2017), and in 2009 there were approximately 548 million dental surgical procedures (Manski and Brown, 2012). Acute pain following surgical care is one of the most common indications for opioid prescribing. Currently, the majority (76% for adult and 60% for children) of opioid-naïve patients undergoing major and minor elective surgery procedures fill an opioid

prescription following surgery, and approximately 9% of opioid-naïve adult patients and 5% of pediatric patients refill prescriptions at least once in the postoperative period (As-Sanie et al., 2017; Harbaugh et al., 2018; Ladha et al., 2019; Sekhri et al., 2018). The committee recognizes that these numbers are likely to decrease in the next several years as opioid prescribing practices change in response to the awareness of opioid-related harms and alternative pain management approaches, the emergence of effective opioid alternatives, and state and organizational limits on opioid prescribing.

Surgical care is often episodic, rather than longitudinal, which has several implications for guidelines for postoperative opioid prescribing. First, because the surgeon may not be involved in the long-term care after the surgery nor manage the entirety of a patient's comorbid conditions and associated medications, care is often transitioned to other providers, such as primary care clinicians. As such, postoperative opioid prescribing requires appropriate coordination with the patient's other health care providers, particularly those providing ongoing care for patients using opioids at the time of surgery or at high risk for chronic pain and chronic opioid use or misuse (Klueh et al., 2018). Moreover, ongoing opioid decisions may be transferred to other providers. For example, many patients undergoing total knee arthroplasty are taking opioids at the time of surgery, and thus primary care providers may bear the burden of postoperative opioids prescribing for ongoing joint pain (Bell et al., 2018). Therefore, when possible, it is important to communicate and plan for opioid prescribing prior to surgical care in order to ensure safe pain management, the avoidance of high-risk prescribing behaviors (e.g., multiple overlapping prescriptions and prescriptions from multiple providers), and the avoidance of ongoing opioid prescribing when other interventions may be preferable or equally effective.

In addition, surgical care presents an important opportunity for quality improvement initiatives. Recent initiatives, such as the use of perioperative antibiotics or venous-thromboembolism prophylaxis, are routinely incorporated into quality metrics by key stakeholders (e.g., health insurers, policy makers, health care organizations, and professional societies) in order to benchmark providers. Because procedures are performed by defined groups or specialties, health care organizations have the opportunity to track pain- and opioid-related outcomes as well as opioid prescribing in order to create best practices, identify outliers, and enhance the safety and quality of postoperative pain management. The committee notes that it found more evidence of variation in opioid prescribing and discrepancies in opioid prescribing, opioid consumption, and pain-related outcomes for surgical procedures than for medical conditions causing acute pain (see Tables 5-2 and 5-3).

Variation in Prescribing for Surgery

In the absence of CPGs, current prescribing often represents a provider's judgment regarding the amount of opioid, if any, a patient will require following surgery. In contrast to chronic pain, opioid prescribing for acute pain following procedural care is typically provided on an as-needed basis. Acute postoperative pain is expected to subside with the resolution of inflammation and with the healing of the tissue, typically within 3 months after the index procedure, although the precise level of pain is dependent on both patient and procedural factors (Schug et al., 2019). As such, the extent of tissue injury may influence opioid prescribing, and patients undergoing larger or more "invasive" surgical procedures (e.g., greater dissection, tissue injury, and length of surgery) may require a greater amount of pain medication than is necessary for less extensive procedures.

In contrast with other types of care for which opioid prescribing has remained flat or declined, there is some evidence that prescribing for surgical, dental, and emergency care has been increasing—according to one study, by 15.8% between 2010 and 2016 ($p<0.001$) (Larach et al., 2018). During this period, outpatient postoperative opioid prescribing among primary care and other specialties decreased by about 9% (Larach et al., 2018). The authors found that the amount per person and the prescribing rate

for high-dosage prescriptions, short-term prescriptions, and extended release and long-acting formulations decreased over that period, whereas the duration and prescribing rate for long-term prescriptions of opioids increased.

Multiple studies have found a wide variation in opioid prescribing within procedures in adults and children (Anderson et al., 2018; As-Sanie et al., 2017; Cartmill et al., 2019; Horton et al., 2019a; Johnson and Makai, 2019; Madsen et al., 2018; Osmundson et al., 2017). Makary et al. (2017) found that following laparoscopic cholecystectomy, opioid prescriptions ranged from zero to more than 50 pills, with only about one-fifth of the surgeons prescribing within institutional prescribing guidelines of ≤10 pills. Variations in opioid prescribing were found for children after anterior cruciate ligament (ACL) repairs, appendectomy, cholecystectomy, and hernia repair (Anandarajan et al., 2019; Denning et al., 2019; Pruitt et al., 2019; Sonderman et al., 2018). Johnson and Makai (2019) described postoperative prescribing following minimally invasive gynecologic surgery as ranging from 125 to 300 oral morphine equivalents. In addition, Ziegelmann et al. (2019) described wide variation within procedure type for patients undergoing open nephrectomy, cystectomy, and retroperitoneal lymph node dissection.

Opioid prescribing may vary by provider type and hospital. In a statewide analysis of hospitals, prescribing was found to vary 4.7-fold across centers, and prescriptions provided by advanced practice providers were 18% higher than prescriptions provided by physicians (Cron et al., 2018, 2019; Lund et al., 2019). Similarly, for surgical care that occurs in teaching hospitals, prescribing may differ between surgeons in training and other prescriber types (Bhashyam et al., 2019; Bicket et al., 2017; Chiu et al., 2018; Cron et al., 2019; Lancaster et al., 2019).

Excessive Prescribing

In addition to demonstrating variation in prescribing, a number of studies have also found excessive opioid prescribing (Cartmill et al., 2019; Horton et al., 2019b; Paulozzi et al., 2014; Sonderman et al., 2018). These studies suggest that efforts to reduce opioid prescribing for postoperative pain so that they align more closely with patient-reported opioid use may yield comparable outcomes with respect to pain, satisfaction, and postoperative quality of life. For example, recent studies suggest that postoperative opioid use can be decreased as a result of provider- and health care–system interventions (Hill et al., 2018b), policy and legislative measures (Dave et al., 2019), and enhancing patient education and engagement in postoperative pain management (Alter and Ilvas, 2017). A recent study of pediatric patients undergoing outpatient surgery found that after the implementation of institutional guidelines, most patients were not prescribed opioids following surgery, did not report opioid use, did not require refills, and that a greater proportion of patients were directed to and used nonopioid alternatives for postoperative pain management (Harbaugh et al., 2018).

Risk of Prolonged Postoperative Opioid Use

Recent studies assessing the risk that opioid-naïve patients, including both adults and children, will transition to prolonged opioid use following surgery have produced probabilities ranging from 1% to 15% (Alam et al., 2012; Clarke et al., 2014; Sun et al., 2016). For example, Sun et al. (2016) found that male sex, age older than 50 years, and a preoperative history of drug abuse, alcohol abuse, depression, benzodiazepine use, or antidepressant use were associated with chronic opioid use among adult surgical patients. The risk factors for persistent opioid use among pediatric surgical patients include older age, female sex, previous substance use disorder, family opioid use, chronic pain, and preoperative opioid use (Harbaugh et al., 2018). Other studies have demonstrated that postoperative opioid use may

be correlated with a number of other patient factors beyond patient-reported pain or procedure type, such as anxiety, mental health conditions, medical comorbidities, and prolonged opioid use, which may not entirely reflect ongoing pain (Badreldin et al., 2018; Brummett et al., 2013; Committee on Practice Bulletins—Obstetrics, 2018; Hilliard et al., 2018; Kelly et al., 2018; Velanovich, 2000). Finally, there is growing evidence that a greater amount of opioid being prescribed prior to or at the time of surgery is correlated with greater opioid consumption and a higher risk of prolonged opioid use (Brummett et al., 2017; Gil et al., 2019; Howard et al., 2018a).

Classification of Surgical Indications

The classification of surgical procedures for creating CPGs for postoperative outpatient opioid prescribing may be framed in multiple ways. In order to facilitate the prioritization of surgical procedures for possible CPG development, the committee sought to categorize procedures into groups that might be most amenable for CPG development. Notably, the committee did not identify any classification frameworks for surgical procedures based on patient attributes, surgical intensity, or tissue injury. The committee believes that such groups would reflect the practicalities of clinical care, which could facilitate the creation and dissemination of a CPG. For example, surgeons often perform multiple types of procedures, and opioid prescribing may not be specific to an individual procedure type. In particular, one study showed that when opioid prescribing for laparoscopic cholecystectomies was reduced, there was a spillover effect of reduced opioid prescribing for other surgeries of similar scope and tissue injury (Howard et al., 2018a), suggesting that guidelines created for one procedure type may have applicability to other procedures. Moreover, observational studies often group procedures together when examining postoperative opioid use and prescribing. For example, recent studies that examined opioid prescribing and use after surgical procedures were often aligned within surgical specialty or by technical approach or grouped by anatomic location (Fleischman et al., 2019; Hill et al., 2017, 2018b; Horton et al., 2019b; Howard et al., 2018b) (see Table 5-1).

In this report the committee chose to align surgical conditions and procedures based on similarities in operative approach (e.g., laparoscopic, open), anatomic region (e.g., abdominal cavity, extremity, thoracic procedures), underlying cause of injury (e.g., sports-related injuries), or where the surgery is performed (e.g., inpatient or outpatient). Each of these attributes may influence the amount and duration of opioids prescribed following surgery, if they are prescribed at all. While discussed individually, in practice these categories are not mutually exclusive, and CPGs may be based on whatever single attribute or combination of attributes that is most clinically relevant. However, creating more granular CPGs for specific surgeries based on procedural nuances may be an opportunity in the future as the knowledge gaps regarding tissue injury, acute pain, and opioid requirements close with future research. For example, laparoscopic cholecystectomy procedures may be performed on an emergency basis or electively and in either inpatient or outpatient settings, and the majority of current evidence has focused only on these performed on an elective, outpatient basis. CPGs developed for elective, outpatient laparoscopic cholecystectomies could be applied to cases performed on an emergency basis or in an inpatient setting, or they could be refined in future work for the nuances of these aspects of clinical care. The section below provides a rationale for the classification of surgical procedures in order to provide clarity on the groups selected for prioritization in the committee's Statement of Task and to inform efforts for future CPG development in which stakeholders may opt to classify procedures differently.

TABLE 5-1 Attributes for Classifying Surgical Procedures for Clinical Practice Guideline Development

Attribute	Examples	Considerations
Surgical approach	Dental, endoscopic, endovascular, laparoscopic, robotic, thoracoscopic, open techniques	Allows for the tailoring of guidelines toward size of incision and extent of soft tissue injury.
Timing of procedure	Elective, emergency, urgent	May capture differences in condition severity, such as inflammation or infection, which may differ by presentation for the same procedure.
Indication	Childbirth, inflammatory processes, malignancy, symptomatology, trauma	May capture the nuances of conditions that supersede approach or anatomic location. May not allow for commonalities across disciplines or techniques regardless of condition.
Anatomic location	Abdominal cavity, abdominal wall, extremity, oral cavity, oropharyngeal	Allows for a broad categorization of procedures beyond condition, surgical discipline, or technique.
Care setting	Inpatient, outpatient, observation	May account for the differences in opioid consumption that may exist based on duration of recovery that occurs within a facility.

Surgical Approach

CPGs for postoperative opioid prescribing also could be considered according to their procedural attributes, including the surgical approach, indications, and anatomic location. For example, CPGs could be created based on the technical approach for the procedure, such the use of open or minimally invasive techniques, including laparoscopic, robotic, endoscopic, and endovascular strategies and dental procedures. Classifying procedures by surgical approach is advantageous in that techniques may better capture the magnitude of tissue injury due to the extent of the incision and dissection. In addition, classification by approach may allow similar procedures to be grouped together. For example, the extent of tissue injury for a laparoscopic hysterectomy may be similar to the tissue injury of a laparoscopic colectomy, and the opioid consumption and pain trajectories identified for certain procedures may translate to other procedures based on operative approach (AJRR, 2017; Kremers et al., 2015). Although the extent to which incision size directly correlates with patient-reported postoperative pain and analgesic use is not well understood, numerous studies have demonstrated that minimally invasive approaches yield faster recovery and less patient-reported pain (Hota et al., 2018; Leach et al., 2018; Theisen et al., 2019). Thus, procedures could be grouped together by operative approach when considering CPGs, such as all laparoscopic abdominal or pelvic procedures being considered under common recommendations (Sloan et al., 2018). This approach may also be clinically intuitive for prescribers, since spillover effects into procedures of similar scope and approach have been observed after implementing opioid prescribing protocols or other enhanced recovery (Bedard et al., 2017; Bicket et al., 2019; Johnson and Makai, 2019; Kahlenberg et al., 2019).

Timing of Procedure

Surgical procedures may also be classified by the timing of intervention, such as elective, urgent, or emergency surgical procedures. Differences in timing may reflect important differences in the severity of

and underlying pathology for surgery. For example, a laparoscopic cholecystectomy performed electively may have far less inflammation and tissue injury related to additional surgical dissection than a procedure performed urgently or in an emergency situation for acute infection, perforation, or gangrenous changes (Mou et al., 2019; Roulin et al., 2016; To et al., 2013). Similarly, an elective hip arthroplasty performed for symptomatic osteoarthritis may differ substantially from a procedure performed for a hip fracture, in which underlying frailty, comorbid conditions, and physical function may create a much different pain trajectory and risk of opioid prescribing following surgery (Charette et al., 2019; Kester et al., 2016; Schairer et al., 2017). Most third molar extractions at an early age (mean age 19 years) are another example of an uncomplicated elective procedure. In contrast, emergency extractions performed for teeth with pulpal and periapical infections that result in a disseminating cellulitis and potential airway obstruction may require more extensive treatment and follow-up (Resnick et al., 2019). Given these nuances in care, the timing and acuity of surgical conditions will inform CPGs for acute pain following surgery.

Indication and Anatomic Location

Surgical procedures could also be classified by the indication for the procedure or anatomic location. For example, procedures could be grouped by anatomic region, such as extremity, torso, or head and neck. The advantages of this approach are that these categories may align with surgical disciplines, such as otolaryngology or gastrointestinal surgery, which are clustered in anatomic regions (Fujii et al., 2018; Johnson and Makai, 2019; Sabatino et al., 2018; Sloan et al., 2018). However, categorizing by anatomic site alone may not capture the extent of tissue injury for procedures, nor the differences in indication, such as malignancy, which may influence the extent of the operation and the expected course of pain and recovery after surgery. In addition, the postoperative pain trajectory may be associated with the type of tissue involved in the procedure. For example, patients undergoing upper extremity procedures involving only skin and soft tissue require fewer opioids than patients undergoing fracture repair or joint procedures (Fujii et al., 2018). Finally, tissue injury, inflammation, pain, and recovery may vary by indication, such as malignancy, inflammation, trauma, degenerative disease, or infectious conditions. For example, patients undergoing breast reconstruction had longer duration of opioid use than patients undergoing benign breast resections, who used more opioids initially but then quit their use more quickly.

Surgical Setting

Finally, from a health care delivery perspective, surgical procedures may be categorized by the setting in which the surgery occurs and the need for an inpatient stay. Postoperative pain requirements may be different for similar procedures performed in either an inpatient or an outpatient setting. For example, patients undergoing total knee arthroplasty may undergo the procedure with a planned inpatient stay, in which both intravenous and oral opioid regimens are available for postoperative pain control and monitored by health care staff. Alternatively, for patients undergoing total knee arthroplasty as an outpatient procedure, postoperative prescribing may need to anticipate the potential pain requirements the patient will experience at home. Therefore, prescribing guidelines may need to address whether the procedure is to be performed in an inpatient or outpatient setting. If the procedure is to be inpatient, the duration of an inpatient hospital stay may be a factor in determining the opioid prescribing regimen, as postoperative pain may decline to levels in which opioids are not necessary at discharge.

Priority Surgical Indications for Clinical Practice Guideline Development

The committee used specific criteria (see Box 5-1) and explored numerous attributes (see Table 5-1) for identifying the groups of common surgical procedures that it considered priorities for the development of evidence-based CPGs. Many of the surgical procedure groupings apply to pediatrics as well as adult populations, including sport-related injuries, spine procedures, laparoscopic abdominal procedures, and thoracic procedures. Despite this overlap between pediatric and adult patients for many of the surgical groupings, the committee did recognize surgical procedures that are generally unique to pediatrics, such as cleft and craniofacial procedures, correction of pectus excavatum, and correction of congenital limb and hip anomalies (e.g., femoral malformations, acetabular osteotomy, leg length discrepancy).

In response to the committee's Statement of Task, the following surgical procedures and the reasons for their grouping are briefly summarized below; information supporting their prioritization is given in Table 5-2.

- Anorectal, pelvic floor, and urogynecologic procedures (vaginal/perineal approach)
- Breast procedures
- Dental surgeries
- Extremity trauma requiring surgery
- Joint replacement
- Laparoscopic abdominal procedures
- Laparoscopic or open abdominal wall procedures
- Obstetric procedures
- Open abdominal procedures
- Oropharyngeal procedures
- Spine procedures
- Sport-related injuries
- Thoracic procedures

In prioritizing the surgical procedures listed in Table 5-2, the committee focused on procedures for which there was evidence of opioid prescribing, noting the possibility of variation in prescribing across providers and in relation to patient-reported outcomes or patient-centered outcomes. The committee notes that several common surgical procedures identified by Steiner et al. (2017) are surgeries for which outpatient postoperative opioid prescribing is exceedingly rare (e.g., cataract surgery, myringotomy, and tympanostomy tube placement); these were thus also determined to be less of a priority for CPG development. For example, Steiner et al. (2017) determined that of the almost 10 million ambulatory or inpatient surgeries performed in 2014, lens and cataract procedures were the most prevalent, at about 1.4 million procedures; however, opioids are rarely prescribed for pain following cataract surgery (Shoss and Tsai, 2013). There are also many surgical procedures performed on infants and children in which opioids are aggressively used both intra- and postoperatively, such as posterior spinal fusion for scoliosis and hip reconstruction for dysplasia, but prospective data are not available to guide subsequent opioid dosing. For example, evidence suggests that opioid alternatives are superior for pain management following myringotomy and tympanostomy tube placement in children, and opioids are rarely prescribed (Pappas et al., 2003).

Table 5-2 details the existing evidence and current guidelines for opioid prescribing for specific indications. These guidelines range from those developed at the institutional level (e.g., Overton et al., 2018) to those at the national level (e.g., Hegmann et al., 2014). For example, Overton et al. (2018) developed consensus recommendations for opioid prescribing after 20 common surgical procedures; stakeholders in this consensus process included surgeons, pain specialists, outpatient nurses, pharmacists, and patients. Other groups, such as the Michigan Opioid Prescribing Engagement Network, have created guidelines on the basis of patient-reported outcomes, specifically patient-reported postoperative opioid use following various procedure types (Vu et al., 2019).

TABLE 5-2 Opioid Prescribing Patterns for Priority Surgical Indications

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Anorectal, pelvic floor, and urogynecologic procedures (vaginal/perineal approach) (e.g., colon resection, hemorrhoidectomy, vaginal hysterectomy)	In 2014, 2.5% of all inpatient surgical procedures were colorectal resections, for a rate of 94.8/100,000 people (McDermott et al., 2017). In 2014, 262,200 (1.5%) of all 17.2 million ambulatory or inpatient surgeries were vulvar, and female pelvic procedures, for a rate of 59.2/100,000 people (Steiner et al., 2017). In 2014, 508,700 (~3.0%) of 17.2 million ambulatory or inpatient surgeries were abdominal and vaginal hysterectomies (Steiner et al., 2017).	42 patients were prescribed an average of 150 OMEs after vaginal hysterectomy, only 50 OMEs were used by patients in the first 2 weeks, and only 4 patients requested opioid refills (As-Sanie et al., 2017). 122 patients were overprescribed by an average of 149%, 165%, and 136% MMEs for sacral neuromodulation, mid-urethral sling, and prolapse repair, respectively; there was a significant reduction ($p<0.001$) in MMEs prescribed after educational intervention (Moskowitz et al., 2019). Among 57 women undergoing pelvic organ prolapse surgery, only 32.8% of prescribed OMEs were consumed; after implementation of prescribing recommendations, total OMEs decreased by 45%, amount of leftover pills decreased ($p<0.0001$), but refills increased ($p=0.03$), with similar satisfaction scores before and after implementation (Linder et al., 2019).	*The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Hemorrhoids*—"Patients undergoing surgical hemorrhoidectomy should use a multimodality pain regimen to reduce narcotic usage and promote a faster recovery" (Davis et al., 2018). Opioid studies were included. *Clinical Practice Guidelines for Enhanced Recovery After Colon and Rectal Surgery from the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons*—"A multimodal, opioid-sparing, pain management plan should be used and implemented before the induction of anesthesia." Minimizing opioid use is associated with earlier return of bowel function and shorter length of stay (Carmichael et al., 2017).

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Breast procedures (e.g., lumpectomy, mastectomy, reconstruction, reduction)	In 2014, 305,600 of 17.2 million ambulatory or inpatient surgeries were lumpectomies (1.8%); 103,500 were mastectomies (0.6%); and 410,100 were therapeutic surgical procedures of skin and breast, including plastic surgery on breast (2.3%) (Steiner et al., 2017).	At 1–2 weeks following mastectomy with immediate reconstruction, 23 patients received median prescriptions of 550 MMEs and 77% of the MMEs were unused with 83% satisfaction; among 27 patients receiving 263 median MMEs, there was 58% MMEs unused with 93% satisfaction; 1 and 2 patients, respectively, required refills (Sada et al., 2019). Of 5,233 TRICARE patients undergoing mastectomy, 31.5% required ≥1 opioid refill (Scully et al., 2018). 10% of 4,113 patients undergoing mastectomy continued to fill an opioid prescription 90 days after surgery (Marcusa et al., 2017).	John Hopkins *Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus*—Developed consensus ranges for outpatient opioid prescribing at the time of discharge for partial mastectomy with or without sentinel lymph node biopsy (Overton et al., 2018).
Dental surgeries (e.g., third molar extraction)	7–10 million procedures per year (Friedman, 2007; Moore et al., 2006). Approximately 68% of all opioids prescribed were during surgical dental visits (Gupta et al., 2018).	93% of 81 patients prescribed oxycodone following third molar extraction used no postoperative pills, with 466 prescribed pills unused or unfilled (Resnick et al., 2019). Prior to implementing an opioid prescribing protocol for third molar extractions, the mean number of opioid pills per prescription was 15.9 in 2015, and in 2017, after implementation it decreased to 11.5 (Tompach et al., 2019).	American Dental Association *Policy on Opioid Prescribing*—Use nonopioids as first-line therapy for acute dental pain (ADA, 2018). Bree Collaborative *Dental Guideline on Prescribing Opioids for Acute Pain Management*—Prescribe nonopioids as first-line therapy (Bree Collaborative, 2017). Center for Opioid Research and Education *Dental Opioid Guidelines*—NSAIDs as first-line therapy (CORE, 2018).

continued

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
			Dionne *Prescribing Opioid Analgesics for Acute Dental Pain: Time to Change Clinical Practices in Response to Evidence and Misperceptions*—Provide a prescription of an opioid drug (3-day supply only) in combination with acetaminophen to be filled and administered only if needed for pain not relieved by regimen for moderately severe pain (Dionne et al., 2016). Wisconsin *Best Practices for Prescribing Controlled Substances Guidelines*—NSAIDs as first-line therapy. "Dentists should prescribe the lowest possible effective dosage. Dentists should avoid prescribing opioid doses >50 mg morphine equivalents per day" (Wisconsin, 2017). *Washington State Opioid Prescribing Requirements*—7-day opioid supply limit, unless clinically documented (Washington, 2018). *Pennsylvania Guidelines on the Use of Opioid in Dental Practice*—NSAIDs for first-line therapy. "If an opioid is to be administered, the dose and duration of therapy should be for a short period of time, and for conditions that typically are expected to be associated with more severe pain" (Pennsylvania, 2018). Michigan *Acute Care Opioid Treatment and Prescribing Recommendations: Dental*—"For breakthrough or severe pain, short-acting opioids (e.g., hydrocodone, oxycodone) should be prescribed at the lowest effective dose for no more than 3 to 5 day courses" (Michigan, 2018).

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Extremity trauma requiring surgery (e.g., amputation, open reduction and internal fixation)	In 2014, 289,800 of 14.2 million operating room procedures were for treatment of fractures or dislocations of the hip and femur (2.0%) (McDermott et al., 2017). In 2014, 518,700 of 17.2 million ambulatory or inpatient surgeries were for treatment of fractures or dislocation of radius, ulna, or lower extremity other than hip or femur (3.0%) (Steiner et al., 2017). In 2014, 181,100 of 17.2 million ambulatory or inpatient surgeries were for amputation of a lower extremity (1.0%) (Steiner et al., 2017). 1/190 Americans have loss of a limb (Ziegler-Graham et al., 2008).	Of 81 children undergoing closed reduction and percutaneous pinning of a supracondylar humeral fracture, IQR of opioid use was 1–7 doses, patients used 24.1% of prescribed opioids (mean, 4.8 doses used and 19.8 doses prescribed) (Nelson et al., 2019). Opioids prescribed after discharge for orthopedic fractures ranged from 20 to 655 mg oxycodone pills; distal radius fractures received the least MMEs compared with other fracture locations in opioid-naïve patients (Bhashyam et al., 2019).	U.S. Department of Veterans Affairs/U.S. Department of Defense *Clinical Practice Guideline For Rehabilitation of Individuals with Lower Limb Amputation*—For lower limb amputation "We suggest offering a multi-modal, transdisciplinary individualized approach to pain management including transition to a non-narcotic pharmacologic regimen combined with physical, psychological, and mechanical modalities throughout the rehabilitation process" (VA/DoD, 2017). Orthopaedic Trauma Association *Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury*—For pain management in acute musculoskeletal injury "prescribe the lowest effective immediate release opioid dose for the shortest period possible" (Hsu et al., 2019). John Hopkins *Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus*—Developed consensus ranges for outpatient opioid prescribing at the time of discharge after 20 common procedures (Overton et al., 2018). American College of Occupational and Environmental Medicine *ACOEM Practice Guidelines: Opioids for Treatment of Acute, Subacute, Chronic, and Postoperative Pain*—"Opioids for treatment of acute, severe pain (e.g., crush injuries, large burns, severe fractures, injury with significant tissue damage) uncontrolled by other agents and/or with functional deficits caused by pain" (Hegmann et al., 2014).

continued

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Joint replacement (e.g., total hip arthroplasty [THA], total knee arthroplasty [TKA])	In 2014, out of 17.2 million ambulatory or inpatient surgeries, there were 789,500 knee arthroplasties (4.5%), 546,000 (3.1%) partial or THA, and 154,800 (0.9%) arthroplasties other than hip or knee (Steiner et al., 2017). In 2010, there were 2.5 million THA and 4.7 million TKA (Kremers et al., 2015). Approximately 680,000 knee replacements yearly (Sloan et al., 2018).	At 1-month follow-up, of 115 patients undergoing spine or joint surgery, 73% reported unused opioid pills, 46% had ≥20 unused pills, and 37% had ≥200 unused MMEs (Bicket et al., 2019). Out of 30,938 opioid-naïve patients undergoing TKA and 13,744 undergoing THA, 27% of TKA patients and 38.5% of THA patients filled no opioid prescription after surgery (Cook et al., 2019). 304 opioid-naïve patients who underwent THA or TKA were randomized to receive either 30 oxycodone immediate release pills or 90 pills at discharge; at 30 days after discharge, patients who received 30 pills had a significantly lower median of 15 (range, 0–30) unused pills compared to a median of 73 (range, 0–90) unused pills for those who received 90 pills ($p<0.001$). Within 90 days of discharge, significantly more ($p<0.001$) patients in the 30-pill group requested a refill compared to 90-pill group (Hannon et al., 2019). Opioids were overprescribed by more than 34% in TKA (n=51) and 140% in THA (n=48); median number of pills prescribed for 30 days was 90, median number of pills consumed was 67 (TKA) and 37 (THA); TKA patients had higher pain scores and were 5 times more likely to require a refill (Huang and Copp, 2019). 64.1% of 66 patients undergoing TKA stopped taking opioids within 6 weeks of surgery and had a mean equivalent of 18 oxycodone 5 mg pills remaining (Premkumar et al., 2019).	American Academy of Orthopaedic Surgeons—*Clinical Practice Guideline on Surgical Management of Osteoarthritis of the Knee*—No mention of opioid prescribing except to say opioid prescribing can be reduced by using anesthesia such as nerve blocks (AAOS, 2015b). American Academy of Orthopaedic Surgeons—*Information Statement: Opioid Use, Misuse, and Abuse in Orthopaedic Practice*—"A prescription should only include the amount of pain medication that is expected to be used/appropriate, based on the protocol established. For patients who live longer distances from their surgeons, two prescriptions for smaller amounts of opioids with specific refill dates should be considered rather than a single large prescription" (AAOS, 2015a).

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Laparoscopic abdominal procedures (e.g., appendectomy, bariatric surgery, cholecystectomy, colectomy, hysterectomy, prostatectomy); see also Open abdominal procedures	In 2014, 2.6% of all inpatient surgeries were cholecystectomy and common duct exploration for a rate of 116.9/100,000 people (McDermott et al., 2017). In 2014, out of 17.2 million ambulatory or inpatient surgeries, 950,100 (5.5%) were cholecystectomy and common bile duct exploration, 447,600 (2.6%) were appendectomies, 32,300 (0.2%) were gastric bypass and volume reduction surgery; and 171,200 (1.0%) were laparoscopic gastrointestinal procedures (Steiner et al., 2017*). It is estimated that there were 228,000 bariatric surgeries in 2017 (ASMBS, 2018).	Among 1,376 opioid-naïve patients undergoing laparoscopic cholecystectomy, 96% received an opioid prescription at discharge with a median of 225 OMEs; 52% were prescribed more than the state draft guideline of 200 OMEs. The 30-day refill rate was 5% (Hanson et al., 2018). Among 2,392 patients undergoing laparoscopic cholecystectomy, appendectomy, or hysterectomy, the median discharge prescription was 150 OMEs (IQR, 135–225), equivalent to 30 pills of hydrocodone/acetaminophen, 5/325 mg; median use was only 30 mg (<10 pills), and 21% of those undergoing cholecystectomy took no opioids. Patients undergoing laparoscopic colectomy were prescribed a median of 40 pills, took a median of fewer than 10 pills, and 34% took no opioids (Howard et al., 2018b). 170 patients who underwent laparoscopic cholecystectomy were compared with 200 patients who underwent the procedure after a hospital intervention to reduce opioid prescribing. Preintervention patients were prescribed a median of 250 OMEs (IQR, 200–300), equivalent to 40 5/325 mg hydrocodone/acetaminophen pills; median use was 30 OMEs (<10 pills); postintervention patients were prescribed a median of 75 OMEs (IQR, 75–112.5) and used 20 OMEs. There was no difference in pain scores between the groups (Howard et al., 2018c).	John Hopkins *Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus*—Developed consensus ranges for outpatient opioid prescribing at the time of discharge after robotic retropubic prostatectomy or laparoscopic cholecystectomy (Overton et al., 2018). *Clinical Practice Guidelines for Enhanced Recovery After Colon and Rectal Surgery from the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons*—"A multimodal, opioid-sparing, pain management plan should be used and implemented before the induction of anesthesia" (Carmichael et al., 2017). Friedman *Postoperative Opioid Prescribing Practices and Evidence-Based Guidelines in Bariatric Surgery*—Recommends outpatient prescriptions of no more than 8–15 pills after common bariatric surgical procedures (Friedman et al., 2019). Hill *Guideline for Discharge Opioid Prescriptions After Inpatient General Surgical Procedures*—Postdischarge opioid use is best predicted by usage the day before discharge from inpatient laparoscopic colectomy or laparoscopic pancreatectomy (Hill et al., 2018a).

continued

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
		A median of 30 pills were prescribed to patients undergoing laparoscopic cholecystectomy and only about 32.7% of the pills were taken (Hill et al., 2017). Among 205 patients undergoing radical prostatectomy, a median of 225 mg OMEs were prescribed and 22.5 mg used, overall 77% of postdischarge opioid medication was unused, with 84% of patients requiring ≤112.5 mg OMEs (Patel et al., 2019). Among patients undergoing laparoscopic prostatectomy, or minimally invasive (i.e., laparoscopic or robotic) partial or radical nephrectomy, the median OME prescribed was 27 for each procedure and the median use (IQR) was 8 (6–20) for minimally invasive nephrectomy and 4 (1–15) for robotic-assisted laparoscopic prostatectomy; overall 60% of the prescribed pills were unused (Theisen et al., 2019). Among 1,892 patients without baseline opioid use prior to bariatric surgery, postoperative opioid use increased from 5.8% (95% CI 4.7–6.9) at 6 months to 14.2% (95% CI 12.2–16.3) at year 7 (King et al., 2017). After discharge following laparoscopic bariatric surgery, 68 patients were prescribed 1,921 opioid pills total; the mean number of pills taken was 650 (33.8%) and 4.4% requested refills (Hill et al., 2018a).	

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Laparoscopic or open abdominal wall procedures (e.g., femoral hernia, incisional hernia, inguinal hernia)	In 2014, out of 17.2 million ambulatory or inpatient surgeries, 477,400 (2.8%) were inguinal and femoral hernia repair, and 614,200 (3.5%) were other hernia repairs (Steiner et al., 2017).	Following inguinal/femoral or open incisional hernia repair, the median OMEs prescribed were 150 (IQR, 135–225; equivalent to 30 pills of hydrocodone/acetaminophen, 5/325 mg); median use was 30 mg (<10 pills) for inguinal/femoral repair, and approximately 15 pills for open incisional repair (Howard et al., 2018b). Among 27 patients undergoing laparoscopic or open ventral hernia repair, 639 opioid pills were prescribed of which 53.4% were taken (Hill et al., 2018a). 39,297 patients received a median initial opioid pain prescription of 6 days following laparoscopic or open inguinal hernia repair and 14.3% received one or more refills (Scully et al., 2018). Patients undergoing laparoscopic or open inguinal hernia repair were prescribed a median of 30 opioid pills and took 14.5% and 31.1% of pills, respectively (Hill et al., 2017). In pediatric patients, postoperative opioid prescriptions were significantly reduced for hernia repair following an educational intervention: 4.2±2.9 versus 2.7±2.6 days' supply (p=0.004) (Horton et al., 2019b).	Society of American Gastrointestinal and Endoscopic Surgeons *Guidelines for Laparoscopic Ventral Hernia Repair*—"Persistent pain following laparoscopic ventral hernia repair should be treated with analgesics, anti-inflammatory medications, steroids, trigger point injection or nerve block" (Earle et al., 2016). No specific mention of opioids. John Hopkins *Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel* Consensus—Developed consensus ranges for outpatient opioid prescribing at the time of discharge after laparoscopic or open inguinal hernia repair, unilateral or umbilical hernia repair (Overton et al., 2018). The HerniaSurge Group *International Guidelines for Groin Hernia Management*—"Opioids can be used for moderate- or high-intensity pain, in addition to non-opioid analgesia or when the combination of an NSAID and paracetamol is not sufficient or is contraindicated" (Simons et al., 2018). Hill *Guideline for Discharge Opioid Prescriptions After Inpatient General Surgical Procedures*—Postdischarge opioid use is best predicted by usage the day before discharge from inpatient laparoscopic or open ventral hernia repair (Hill et al., 2018a).

continued

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Obstetric surgeries (e.g., cesarean delivery, vaginal delivery)	Cesarean sections were the most frequent operating room procedure in 2014, with 1,242,800 procedures out of 14,198,000 inpatient procedures, for an incidence of 389.8/100,000 people (McDermott et al., 2017). 3,855,500 births annually; 32% cesarean; 68% vaginal; 9% have severe perineal laceration; 2.6 million vaginal deliveries annually (ACOG, 2018a; Martin et al., 2018a). In 2017, there were 1,232,339 cesarean deliveries and 2,621,010 vaginal deliveries (Martin et al., 2018a).	Of 165 women who had cesarean deliveries, 83% filled an opioid prescription (median 225 MMEs prescribed) and 75% had unused pills (median 75 MMEs) at 2 weeks postpartum (Osmundson et al., 2017). Of 308,226 deliveries, 27% of women with vaginal deliveries and 75.7% of women with cesarean deliveries filled peripartum opioid prescriptions (Peahl et al., 2019). Of 1.3 million women who had vaginal deliveries, 28.5% were prescribed an opioid (median dose 150 MMEs) within 1 week of discharge; 8.5% of women filled ≥1 opioid prescriptions 6 weeks after delivery (Prabhu et al., 2018). Of 30 patients undergoing cesarean sections, 53% reported taking either no or very few (less than 5) prescribed opioid pills; 83% reported taking half or less; and 17% of women reported taking all or nearly all (5 or fewer pills left over) (Bartels et al., 2016).	The American College of Obstetricians and Gynecologists *ACOG Committee Opinion: Postpartum Pain Management*—Contains recommendations on the use of opioids for postpartum pain and at discharge from the hospital and types of opioids to be used in stepped care (ACOG, 2018a). John Hopkins *Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus*—Developed consensus ranges for outpatient opioid prescribing at the time of discharge for uncomplicated vaginal and cesarean delivery (Overton et al., 2018). Mills *Draft Opioid-Prescribing Guidelines for Uncomplicated Normal Spontaneous Vaginal Birth*—"Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for patients undergoing normal spontaneous vaginal delivery with no complications. 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" (Mills et al., 2019).

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Open abdominal procedures (e.g., appendectomy, cholecystectomy, colectomy, hysterectomy); see also Laparoscopic abdominal procedures	In 2014, 508,700 (~3.0%) of 17.2 million ambulatory or inpatient surgeries were abdominal and vaginal hysterectomies (Steiner et al., 2017). In 2014, out of 17.2 million ambulatory or inpatient surgeries, 950,100 (5.5%) were cholecystectomy and common bile duct exploration, 447,60 (2.6%) were appendectomies, 32,300 (0.2%) were gastric bypass and volume reduction surgery, and 9,950,759 were open abdominal surgery (Steiner et al., 2017). Between 2009 and 2013, there were nearly 10 million discharges associated with open abdominal surgery (Carney et al., 2017).	104 patients undergoing open colectomy were prescribed a median of 40 5/325 mg hydrocodone/acetaminophen pills and took a median of fewer than 15 pills (Howard et al., 2018b). After laparoscopic, open, or robotic colectomy, 69 patients were prescribed 1,022 opioid pills total at discharge; the mean number of pills taken was 201 (19.7%) and 2.9% requested refills; after hepatectomy or laparoscopic or open pancreatectomy, patients used 53.6% and 37.3%, respectively, of their prescribed opioids (Hill et al., 2018a). Of TRICARE beneficiaries who underwent an open or laparoscopic appendectomy, 13.6% requested a refill; among those with an open or laparoscopic cholecystectomy, 11.3% requested a refill; and among those with an open, vaginal, or laparoscopic hysterectomy, 17.3% requested a refill. All refill requests were made within 7–8 days of the initial prescription (Scully et al., 2018). Among patients undergoing open nephrectomy or radical prostatectomy, the median OME prescribed was 27 for each procedure, and median use (IQR) was 14 (2–22) and 9 (4–23), respectively; overall 60% of pills prescribed went unused (Theisen et al., 2019).	Society of Gynecologic Surgeons *Preemptive Analgesia for Postoperative Hysterectomy Pain Control: Systematic Review and Clinical Practice Guidelines*—"If using narcotics, we suggest using higher preemptive doses to result in lower postoperative narcotic requirements" (Steinberg et al., 2017). John Hopkins *Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus*—Developed consensus ranges for outpatient opioid prescribing at the time of discharge for open or minimally invasive hysterectomies (Overton et al., 2018). *ACOG Committee Opinion Perioperative Pathways: Enhanced Recovery After Surgery*—Oral opioids if needed; breakthrough pain hydromorphone (ACOG, 2018b). (Note: Specific surgical procedures are not given.) Society for Surgery of the Alimentary Tract (SSAT) *Evidence-Based Current Surgical Practice: Calculous Gallbladder Disease*—No mention of opioids (Duncan and Riall, 2012). Hill *Guideline for Discharge Opioid Prescriptions After Inpatient General Surgical Procedures*—Postdischarge opioid use is best predicted by usage the day before discharge from inpatient open pancreatectomy or open colectomy (Hill et al., 2018a).

continued

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Oropharyngeal procedures (e.g., tonsillectomy)	In 2014, out of 17.2 million ambulatory or inpatient surgeries, 383,300 (2.2%) were tonsillectomy and/or adenoidectomy (Steiner et al., 2017). 339,000 ambulatory tonsillectomies in 2010 (Kou et al., 2019).	Of 64 patients who underwent tonsillectomy, 67.2% reported unused opioids; mean MME prescribed per day was 74.1±44.8, with a mean MME used per day of 49.2±34.3, resulting in 228.1±208.5 MMEs remaining per patient (Choo et al., 2019). After an educational intervention for providers, there was no reduction in the amount of opioids prescribed for pediatric patients undergoing tonsillectomy: 6.3±4.4 versus 5.4±3.0 days' supply (p=0.226) (Horton et al., 2019b).	American Academy of Otolaryngology–Head and Neck Surgery *Clinical Practice Guideline: Tonsillectomy in Children (Update)*—If opioids are used in the immediate postoperative period, they should be used at reduced doses with careful titration and continuous pulse oximetry. Studies have demonstrated that NSAIDs decrease postoperative pain, nausea, and vomiting and are a "viable alternative to opioids. Clinicians must not administer or prescribe codeine, or any medication containing codeine, after tonsillectomy in children younger than 12 years" (Mitchell et al., 2019). John Hopkins *Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus*—Developed ranges for outpatient opioid prescribing at the time of discharge for partial or total thyroidectomy or for cochlear implant (Overton et al., 2018).

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Spine procedures (e.g., fusion in both adults and children, laminectomy)	3.3% of all inpatient surgical procedures in 2014 were spinal fusions, for a rate of 145.3/100,000 people; 3.1% were laminectomies, 137.4/100,000 people (McDermott et al., 2017). In 2014, out of 17.2 million ambulatory or inpatient surgeries, 500,900 (2.9%) were spinal fusions (Steiner et al., 2017).	After implementation of an opioid prescribing guideline, the mean amount of opioids prescribed after lumbar spine surgeries dropped from 629 OMEs (81 pills) to 490 OMEs (66 pills); the mean number of prescribed pills also decreased (81 versus 66, $p<0.001$); however, refill rates within 6 weeks were higher (7.6% versus 12.4%, $p<0.07$) (Lovecchio et al., 2019). Of 16,647 TRICARE patients undergoing discectomy, 30.1% required ≥1 opioid refills (Scully et al., 2018). Of 81 patients undergoing spine or joint surgery, at 1-month postsurgery, 73% reported having unused opioid pills, 46% had ≥20 unused pills, and 37% had ≥200 MMEs (Bicket et al., 2019). Between 2007 and 2014, opioid prescribing in the first 30 days after a laminectomy varied dramatically across states from fewer than 2,000 MMEs in most states to more than 2,000 MMEs in 10 states (73,176 patients) (Vail et al., 2018).	*ACOEM Practice Guidelines: Opioids for Treatment of Acute, Subacute, Chronic, and Postoperative Pain*—Routine use of opioids for treatment of acute pain is strongly not recommended. Opioids may be used for treatment of acute, severe pain (e.g., crush injuries, large burns, severe fractures, injury with significant tissue damage) uncontrolled by other agents and/or with functional deficits caused by pain. "The maximum daily oral dose recommended for opioid-naïve, acute pain patients based on risk of overdose/death is 50-mg MED." Recommend taper off opioid use in 1 to 2 weeks (Hegmann et al., 2014).

continued

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Sports-related procedures (e.g., ACL repair and reconstruction, joint arthroscopy, rotator cuff repair)	In 2014, out of 17.2 million ambulatory or inpatient surgeries, 106,700 (0.6%) were arthroscopic procedures and 1,050,900 (6%) were therapeutic surgical procedures on muscle, tendon, and soft tissue (Steiner et al., 2017). Rate of ACL reconstruction increased 22%, from 61.4/100,000 person-years in 2002 to 74.6/100,000 person-years in 2014; highest rates were among adolescents aged 13–17 (Herzog et al., 2018).	100 patients undergoing shoulder surgery (rotator cuff repair, labral repair, stabilization/Bankart repair, debridement) received 60 opioid pills at discharge; at postoperative day 90, the total number of prescribed pills was 4,480, the total number of unused pills was 1,628, and an overall median of 13 pills remained (Kumar et al, 2017). Among 16,511 TRICARE patients undergoing ACL repair and 14,840 undergoing rotator cuff repair, 39.3% and 36.0%, respectively, required ≥1 opioid refill (Scully et al., 2018). At 3 months after ACL reconstruction, 7.24% of 4,946 patients were still filling opioid prescriptions (Anthony et al., 2017). Among 70 patients who underwent a preoperative opioid education intervention, there was a statistically significant decrease in opioid consumption at 2 weeks (average 19%, p=0.1), 6 weeks (33%, p=0.02), and 3 months (42%, p=0.01) follow-up compared with controls (Syed et al., 2018).	John Hopkins *Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus*—Developed consensus ranges for outpatient opioid prescribing at the time of discharge after arthroscopic partial meniscectomy, arthroscopic ACL/PCL repair, arthroscopic rotator cuff repair, and open reduction and internal fixation of the ankle (Overton et al., 2018). American College of Occupational and Environmental Medicine *ACOEM Practice Guidelines: Opioids for Treatment of Acute, Subacute, Chronic, and Postoperative Pain*—Opioids for treatment of acute, severe pain (e.g., crush injuries, large burns, severe fractures, injury with significant tissue damage) uncontrolled by other agents and/or with functional deficits caused by pain (Hegmann et al., 2014). Orthopaedic Trauma Association *Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury*—Prescribe the lowest effective immediate release opioid dose for the shortest period possible (Hsu et al., 2019). AAOS *Management of Anterior Cruciate Ligament Injuries Evidence-Based Clinical Practice Guideline*—No mention of opioids (AAOS, 2014a). AAOS *Management of Rotator Cuff Injuries Evidence-Based Clinical Practice Guideline*—"Moderate strength evidence supports the use of multimodal programs or nonopioid individual modalities to provide added benefit for postoperative pain management following rotator cuff repair" (AAOS, 2019).

TABLE 5-2 Continued

	Criteria for Developing Clinical Practice Guidelines		
Procedure Groups and Examples	Prevalence of Procedure	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
			Pennsylvania *The Safe Prescribing of Opioids in Orthopedics and Sports Medicine*—"Opioids should rarely be used as the only analgesic. Pain care can include non-opioid medications, regional anesthesia, and various modalities of therapeutic and supportive care." Opioids should be limited to 7-day dosage in some situations according to 2016 Pennsylvania laws (Pennsylvania, 2017).
Thoracic procedures (e.g., thoracoscopy, repair of pectus excavatum in children [Nuss procedure])	Pectus chest deformities occur in approximately 1 of every 300 to 400 white male births and occurs 5 times more often in men than women (Jaroszewski et al., 2010). The prevalence of pectus excavatum is 2.6% in children ages 7 to 14 yrs (Abdullah and Harris, 2016).	Among children undergoing inpatient surgery, the median number of opioid doses dispensed was 43 (IQR, 30–85 doses) with a median duration of 4 days (IQR, 1–8 days); children who underwent orthopedic or Nuss surgery consumed 25.42 (95% CI 19.16–31.68) more doses than those who underwent other types of surgery ($p<0.001$). Overall 58% (95% CI 54–63%) of doses were not consumed (Monitto et al., 2017). Among 31 patients undergoing thoracic surgery, 45% reported taking either no or very few (5 or less) prescribed opioid pills; 71% reported taking half or less; and 29% of patients reported taking all or nearly all (5 or fewer pills left over) of their opioid prescription (Bartels et al., 2016).	John Hopkins *Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus*—Developed consensus ranges for outpatient opioid prescribing at the time of discharge for video-assisted thoracoscopic wedge resection (Overton et al., 2018).

***** For most inpatient or ambulatory surgeries, Steiner et al. (2017) do not indicate whether the surgery was open or laparoscopic; where the type of surgery was specified this is reported.

NOTE: ACL=anterior cruciate ligament; CI=confidence interval; CPG=clinical practice guideline; IQR=interquartile range; MME=morphine milligram equivalent; NSAID=nonsteroidal anti-inflammatory drug; OME=oral morphine equivalent; THA=total hip arthroplasty; TKA=total knee arthroplasty.

MEDICAL INDICATIONS OVERVIEW

Acute pain may be ascribed to a number of medical conditions, ranging from relatively common conditions such as back pain to less frequently occurring conditions such as sickle cell disease. However, in contrast to the burgeoning literature on the use of opioids to treat postoperative or procedural pain, there is less evidence about opioid prescribing for specific medical conditions, about the over- and under-prescribing of opioids for those conditions, and about the outcomes for different opioid prescribing strategies.

The time course of resolution for medical conditions that produce acute pain is variable, and it depends on the etiology of the pain; the natural history of acute pain in the condition; patient factors, such as comorbidities, tolerance, and expectations of pain; and whether definitive treatment is available and used. Furthermore, in some conditions for which opioids are not a first-line treatment, certain patients may not have the expected alleviation of pain by nonopioid treatments (David Jevsevar, Dartmouth Geisel School of Medicine, presentation to committee, July 9, 2019). For such patients, prescribing opioids as a second-line treatment approach may be indicated.

Opioid prescribing for acute pain for medical conditions may occur in primary care clinics, emergency departments (EDs), inpatient hospital settings, and specialty practices such as pain clinics and practices devoted to rheumatology, urology and nephrology, neurology, or orthopedics. Kea et al. (2016) found that the pain-related diagnoses for which opioids were most frequently prescribed in the ED were renal stones (62% of patients received an opioid prescription), neck pain (52%), dental/jaw pain (50%), fracture (49%), cholelithiasis (48%), and back pain (45%). Conversely, among patients prescribed an opioid in the ED, the six most common pain-related diagnoses were non-fracture injuries (29%), back pain (10.5%), fractures (9.5%), abdominal pain (8.3%), dental/jaw pain (6%), and headache (4%). Hudgins et al. (2019) examined trends in opioid prescribing for adolescents and young adults in ambulatory care settings from 2005 to 2015 using data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) and the National Ambulatory Medical Care Survey (NAMCS). They found that 5.2% of visits were associated with an opioid prescription, of which nearly 56% were provided in EDs and another 43% were provided in outpatient clinics. The rates of opioid prescribing were the highest for ED visits by young adults. The most common diagnoses resulting in an opioid prescription in the ED were dental pain and acute injuries among adolescents and dental pain and low back pain among young adults.

In another study that examined opioid prescribing in 19 EDs during 1 week in 2012, there were 19,321 discharges, of which 17.0% received an opioid prescription. The 10 most common diagnoses associated with a discharge opioid prescription were musculoskeletal back pain (10.2%), abdominal pain (10.1%), extremity fracture (7.1%), extremity sprain (6.5%), dental/oral issue (6.2%), other extremity pain (5.8%), nephrolithiasis (4.5%), skin contusion (3.9%), chest pain (including non-cardiac; 3.3%), and closed head injury (3.0%) (Hoppe et al., 2015b).

Mundkur et al. (2019) characterized patterns of opioid analgesic use for acute pain in primary care settings using commercial insurance claims data from 2014. They found that in 2014, 9.1% of patients presenting at their first visit for pain began opioids at that visit. The rate of initiation varied substantially by the reason for the pain; in this study, patients with a history of prior opioid fills were excluded. Among patients with an acute pain complaint, nearly 8% filled an opioid prescription. The authors examined 10 common acute pain conditions selected on the basis of the frequency of their occurrence in the authors' dataset. The conditions, in order of descending prevalence, were joint pain (4.9% filled an opioid prescription); back pain without radiculopathy (13.4% filled an opioid prescription); headache (3.5% filled an opioid prescription); neck pain (9.2% filled an opioid prescription); tendonitis/bursitis (3.4% filled an opioid prescription); muscle strain/sprain (9% filled an opioid prescription); back pain with radiculopathy (17.4% filled an opioid prescription); renal stones (14.2% filled an opioid prescription);

musculoskeletal injury (e.g., ligament tear) (5.8% filled an opioid prescription); and dental pain (27.6% filled an opioid prescription). The authors found that the initial opioid prescription duration was not consistently associated with refill rate, suggesting that for these common medical conditions opioids may be overprescribed. Thus, opioid prescribing for acute medical conditions, like postsurgical care, requires a health care provider's judgment regarding the appropriate dose and duration of opioid.

Chung et al. (2018) analyzed outpatient opioid prescription data among children and adolescents enrolled in Tennessee Medicaid from 1999 to 2014. The annual mean prevalence of opioid prescriptions was 15%. The conditions most commonly associated with an opioid prescription were dental procedures (31.1% prescriptions), outpatient procedure or surgery (25.1%), trauma (18.1%), and infections (16.5%). One out of every 2,611 opioid prescriptions (437 of 1,362,503 total prescriptions) was related to an opioid-adverse event; 71.2% of the adverse events were related to the therapeutic use of the opioid versus abuse or intentional harm.

Methods for Identifying Priority Medical Conditions for Clinical Practice Guideline Development

The committee used several approaches to identify medical indications for priority CPG development. To prioritize medical conditions for CPG development, the committee selected and considered the same key factors (see Box 5-1) that it used to prioritize surgical procedures, for example, the prevalence of the condition, evidence of over-prescribing or under-prescribing of opioids for the condition, and the lack of a CPG or an evidence-based CPG.

The committee began by reviewing a Centers for Disease Control and Prevention (CDC) data analysis of the 2016 NHAMCS ED diagnoses that are associated with a discharge opioid prescription for acute pain (Schappert and Rui, 2019). The committee asked CDC to provide a list of the primary diagnoses for all ED visits at which opioids were prescribed at discharge.

The committee then reviewed the literature to identify data on opioid prescribing in the primary care setting. Although there were numerous studies that looked at opioid prescribing for individual medical indications, the committee found two published studies that examined the prevalence of medical conditions and associated opioid prescriptions for acute pain and thus were useful in prioritizing medical indications for the purposes of the committee. One study analyzed data from NAMCS on opioid prescribing in the primary care setting (Sherry et al., 2018). NAMCS is a national, annual survey of visits made to nonfederally employed, office-based physicians who are primarily engaged in direct patient care and of visits to community health centers; the survey collects information on patient, provider, and visit characteristics (CDC, 2019). Another useful study analyzed administrative data from Optum's Clinformatics™ DataMart on the prevalence of medical conditions and associated opioid prescriptions in the primary care setting (Mundkur et al., 2019). This database is derived from commercial insurance claims that contains a combination of inpatient and outpatient claims, pharmacy dispensing information, and patient demographics routinely collected during health insurance enrollment. In addition, the committee received input from a variety of experts at its public session on priority medical and surgical conditions to be considered for CPG development. Finally, the committee used the expertise of its members not only to review the medical indications that were relatively prevalent and strongly associated with opioids, but also to identify less common medical indications related to acute pain that might be worthy of CPG development based on such factors as evidence of under-prescribing, disproportionate impact on certain populations (e.g., children and adolescents, minorities, older adults), or a strong association with over-prescribing and opioid misuse.

The committee further refined the list of medical indications by removing indications that were overly broad, such as undifferentiated abdominal pain, neck pain, and chest pain. In the committee's judgment it would be difficult to develop an evidence-based CPG at present for such poorly defined indications because their causes can be diverse or unknown and numerous medical specialties may be involved in treating the indication, making it difficult to direct the CPG to a specific medical practice area. For example, in the Mundkur et al. (2018) study, 27 *International Classification of Diseases, Ninth Edition* codes were used to identify neck pain. Preliminary literature searches for these broadly termed indications did not result in substantive articles on the prevalence of the indication and opioid prescribing patterns for the indication. The lack of specific evidence for these indications made them poor candidates for the committee's task.

Of note, the issue of the prevalence of opioid prescribing and the relative distribution of medical conditions in which opioids are prescribed is not consistently studied, as different investigators do not always describe their selection of conditions to consider or define the painful conditions in exactly the same way. In addition, the terminology used to describe and categorize medical conditions is inconsistent across studies. Therefore, the committee grouped related terms together—for example, the committee considered low back pain (the term it uses) to include lumbago, back pain, backache, unspecified dorsalgia, and unspecified low back pain—all of them with or without radiculopathy. This variation in terminology and selection criteria added to the difficulty in determining both prevalence and opioid prescribing practices for an indication.

After the list of potential medical indications was developed, the committee sought evidence on prescribing opioids for each indication. This search was not exhaustive, but rather it focused on recent literature that demonstrated that opioids were prescribed for the indication in the ED, primary care setting, or other health care clinic outside of a surgical setting. For those conditions for which such evidence was available, the committee then sought some evidence of over- or under-prescribing, as such evidence would suggest that evidence-based CPGs might reduce inappropriate practice variation. In addition, the committee sought evidence of new chronic opioid use in opioid-naïve patients who received an opioid prescription for the acute indication. Again, this search was not extensive; a single, well-conducted study showing data on leftover pills or refills was deemed to be sufficient to show that over- or under-prescribing had occurred and that the area warranted further investigation.

Finally, the committee considered whether there was a guideline available on prescribing opioids for acute pain associated with the selected indications. A literature search was conducted to identify any such guidelines (see Appendix B). Although there is considerable guidance available for some indications, little is specific for acute pain or opioid prescribing. Thus, as with surgical procedures, the committee did not identify any CPGs that contain specific recommendations for prescribing opioids to treat acute pain for the specific priority medical indications identified by the committee, although several of them do provide guidances on opioid therapy in the ED or inpatient settings (e.g., NHBLI, 2014). The committee has indicated what guidelines exist and their specificity in Table 5-3. Based on the above information, the committee recommends that CPGs for opioid prescribing be considered for the following medical conditions (see Table 5-3).

- Dental pain (non-surgical)
- Fractures
- Low back pain (includes lumbago, dorsalgia, backache)
- Migraine headache
- Renal stones (also called kidney stones, nephrolithiasis, calculus of the kidney, renal colic)
- Sickle cell disease
- Sprains and strains, musculoskeletal
- Tendonitis/bursitis

TABLE 5-3 Opioid Prescribing Patterns for Selected Medical Indications

	Criteria for Developing Clinical Practice Guidelines		
Indication	Prevalence of Medical Indication	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Dental pain (non-surgical)	Approximately 31% of all opioids prescribed for dental patients were for nonsurgical dental visits, mostly restorative procedures; opioid prescription rate in 2015 for all dental patients was 147.44/1,000 patients. In 2012, dentists prescribed 6.4% of opioids in the United States (Gupta et al., 2018). In 2016, there were 1.68 million visits to EDs with a primary diagnosis of diseases of the teeth and supporting structures (Schappert and Rui, 2019).	The opioid prescription rate per 1,000 dental patients increased from 130.58 in 2010 to 147.44 in 2015; for those aged 11–18 years opioid prescriptions increased from 99.71 in 2010 to 165.94 in 2015; median day supply was 3 days with a median daily dose of 33.33 MMEs for all age groups, but was 37.50 MMEs for ages 19–25 years and 36.00 for ages 11–18 years (Gupta et al., 2018). Before the implementation of a hospital ED opioid prescribing guideline in Maine, the opioid prescribing rate for dental pain was 59%; after implementation the rate was 42% (Fox et al., 2013). In 2016, 53.8% of all patients in the ED with a primary diagnosis of diseases of the teeth and supporting structures were prescribed opioids at discharge (Schappert and Rui, 2019).	No evidence-based CPG available. American Academy of Pediatric Dentistry *Policy on Acute Pediatric Dental Pain Managemen*t—Nonopioid analgesics as first-line agents for pain management; combining opioid analgesics with NSAIDs or acetaminophen for moderate/severe pain may decrease overall opioid consumption (AAPD, 2018). American Dental Association *Policy on Opioid Prescribing*—Supports statutory limits on opioid dosage and duration of no more than 7 days for acute pain (ADA, 2018). Michigan Opioid Prescribing Engagement Network *Acute Care Opioid Treatment and Prescribing Recommendations: Summary of Selected Best Practices*—For breakthrough or severe pain, short-acting opioids (e.g., hydrocodone, oxycodone) should be prescribed at the lowest effective dose for no more than 3- to 5-day courses (Michigan, 2018). *Washington State Opioid Prescribing Requirements for Dentists*—Seven-day opioid supply limit, unless clinically documented (Washington, 2018). Wisconsin *Dentistry Examining Board Best Practices for Prescribing Controlled Substances Guidelines*—Lowest possible effective dosage; avoid prescribing opioid doses >50 mg MME/d; recognize that opioid doses ≥90 mg MME/d dramatically increase risk and therefore require justification and documentation (Wisconsin, 2017).

continued

TABLE 5-3 Continued

	Criteria for Developing Clinical Practice Guidelines		
Indication	Prevalence of Medical Indication	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Fractures	In Olmstead County, Minnesota, between 2009–2011 there was a fracture incidence of 2,704/1000,000 person-years in residents aged ≥50 years (Amin et al., 2014). Age-related (i.e., osteoporosis) fractures in people ≥50 years of age are projected to increase nationally from ≥2 million in 2005 to ≥3 million fractures in 2025 (Burge et al., 2007). In 2016, 2.5% of all ED visits were for traumatic fractures (Schappert and Rui, 2019).	Of 4,600 patients who received nonsurgical treatment for ankle fracture, 48.8% had filled at least one opioid prescription, and 7.4% of them had new, persistent opioid use at 6 months posttreatment (Gossett et al., 2019). Postgraduate second-year residents prescribed more opioid doses to pediatric ED patients with acute injuries, of which 71% were fractures than did other residents or nonresident prescribers (Kahl et al., 2019). In 2016, discharge opioid prescriptions were provided to between 33–53% of ED patients diagnosed with a traumatic fracture (Schappert and Rui, 2019).	No evidence-based CPG or other guidelines available. There are CPGs that focus on surgery for hip fractures in adults (AAOS, 2014b; NICE, 2017).
Low back pain	Among office visits with a pain diagnosis at which opioids were prescribed between 2006–2015, 6.9% were prescribed for lumbago and 3.7% were prescribed for unspecified backache (Sherry et al., 2019).	Opioids were prescribed at discharge for 603,000 (45.5%) ED visits for low back pain and at 968,000 (33.5%) ED visits for other conditions of the spine and back (Schappert and Rui, 2019).	American College of Physicians *Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline*—No evidence to support the use of opioids for acute low back pain (Chou et al., 2017). American College of Physicians *Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline from the American College of Physicians*—As most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select nonpharmacologic treatment (Qaseem et al., 2017).

TABLE 5-3 Continued

	Criteria for Developing Clinical Practice Guidelines		
Indication	Prevalence of Medical Indication	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
	Back symptoms were the fifth most common reason for an ED visit in 2016, and comprised 2.5% of all ED visits (Rui et al., 2016). In 2016, 0.9% (1.3 million visits of 145.6 million total ED visits) of patients received a diagnosis of unspecified low back pain and about 2% received a diagnosis for other conditions of the spine and back, excluding low back pain (Schappert and Rui, 2019).	Opioid prescribing for low back pain was less prevalent in the Northeast (33%) than in other regions of the United States (41%, 43%, 44% in the Midwest, South, and West, respectively, p=0.001) (Morris et al., 2019). Among 23 ED prescribers discharging patients with low back pain, there was a 6-fold variation in the adjusted, risk-standardized prescribing rates that ranged from 12.0% to 78.2% (mean 50.4% [standard deviation +/–16.4]) (Morris et al., 2019).	Kaiser Permanente *Non-specific Back Pain Guideline*—Opioids are rarely indicated for the treatment of back pain. Opioid prescriptions for acute back pain, if made, should be limited to 3 days and follow-up with the patient (Kaiser Permanente, 2017). Institute for Clinical Systems Improvement *Health Care Guideline: Adult Acute and Subacute Low Back Pain*—Opioids are not recommended for acute and subacute low back pain; if nonopioid options have been tried and unsuccessful, the first opioid prescription for acute pain should be the lowest possible effective strength of a short-acting opioid, not to exceed 100 MMEs total. Patients should be instructed that 3 days or less will often be sufficient (ICSI, 2018). American College of Emergency Physicians *Clinical Policy: Critical Issues in the Prescribing of Opioids for Adult Patients in the Emergency Department*—If opioids are indicated, the prescription should be for the lowest practical dose for a limited duration (e.g., <1 week), and the prescriber should consider the patient's risk for opioid misuse, abuse, or diversion (Cantrill et al., 2012).
Migraine headache	1-year period prevalence of migraines is about 18% in women and 6% in men; prevalence peaks between the ages of 25 and 55 (AHS, 2019).	In 2016, 0.4% of ED patients who received a discharge prescription for opioids had a primary diagnosis of migraine (Schappert and Rui, 2019).	American Academy of Neurology *Practice Parameter: Evidence-Based Guidelines for Migraine Headache (an Evidence-Based Review): Report of the Quality Standards Subcommittee of the American Academy of Neurology*—"Butorphanol nasal spray for some migraines; parenteral opiates as rescue therapy for acute migraine if sedation side effects not a risk" (Silberstein, 2000).

continued

TABLE 5-3 Continued

	Criteria for Developing Clinical Practice Guidelines		
Indication	Prevalence of Medical Indication	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
	In 2016, there were more than 4 million visits to EDs for headaches (although not specifically for migraines) (Rui et al., 2016).	A migraine treatment algorithm for ED clinicians reduced the number of patients discharged with opioid prescriptions from 37% to 12.2% (p=0.008) within 6 months of the implementation of the algorithm with further reductions in opioid prescribing to 6% 1 year after implementation (Ahmed et al., 2017).	American Academy of Neurology *Evidence-Based Guideline Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society*—Does not mention opioids (Silberstein et al., 2012). American Academy of Neurology *Practice Guideline Update Summary: Acute Treatment of Migraine in Children and Adolescents*—"No more than 9 days per month of any combination of triptans, analgesics, or opioids for more than 3 months to avoid medication overuse headache. There is no evidence to support the use of opioids in children with migraine. Opioids are included in this statement to be consistent with the International Classification of Headache Disorders regarding medication overuse" (Oskoui et al., 2019). American Headache Society *The American Headache Society Position Statement on Integrating New Migraine Treatments into Clinical Practice*—Recommends against use of opioid, specifically butorphanol (AHS, 2019). Institute for Clinical Systems Improvement *Health Care Guideline: Diagnosis and Treatment of Headache*—Avoid the use of opiates and barbiturates in the treatment of headache (Beithon et al., 2013). Institute of Health Economics, Alberta, Canada, *Primary Care Management of Headache in Adults: Clinical Practice Guideline*—"Opioid analgesics (e.g., codeine, tramadol) and combination analgesics containing opioids are not recommended for routine use for the treatment of migraine because of their potential for causing medication-overuse headache. Opioids may be necessary when other medications are contraindicated or ineffective, or as a rescue medication when the patient's usual medication has failed" (IHE, 2016).

TABLE 5-3 Continued

	Criteria for Developing Clinical Practice Guidelines		
Indication	Prevalence of Medical Indication	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Renal stones	Based on 2007–2010 NHANES, overall prevalence of renal stones was 8.8% (95% CI 8.1–9.5), 10.6% among men (95% CI 9.4–11.9), and 7.1% (95% CI 6.4–7.8) among women (Scales et al., 2012). In 2016, there were 981,000 visits to the ED for calculus of the kidney and ureter (Schappert and Rui, 2019).	An ED opioid-reduction initiative reduced discharge opioid prescribing by 25.5% (95% CI 22.26–28.72), from 68.6% in the 2012–2014 preimplementation phase to 43.1% in the 2015–2017 postimplementation phase (Motov et al., 2018). In 2016, 63.7% of ED patients with a primary diagnosis of calculus of the kidney or ureter received a discharge prescription for opioids (625,000/981,000) (Schappert and Rui, 2019).	American Urology Association *Medical Management of Kidney Stones: AUA Guideline*—No mention of opioids (Pearle et al., 2014). American College of Physicians *Dietary and Pharmacologic Management to Prevent Recurrent Nephrolithiasis in Adults: A Clinical Practice Guideline from the American College of Physicians*—No mention of opioids (Schappert and Rui, 2019). European Association of Urology *Urolithiasis Guidelines*—Offer opiates (hydromorphine, pentazocine, or tramadol) as a second choice (Türk et al., 2016).
Sickle cell disease (SCD)	It is estimated that 100,000 people in the United States have SCD (CDC, 2017). SCD occurs among an estimated 1 out of every 365 black or African-American births and among approximately 1 out of every 16,300 Hispanic-American births (CDC, 2017).	In 2009–2014, opioids used by 39.9% of patients with SCD, most used 0–5 mg OME daily, but 3% of children and 23% of adults used more than 30 mg OME daily; vaso-occlusive crisis and avascular necrosis were associated with high-dose opioid use (Han et al., 2018).	National Heart, Lung, and Blood Institute (NHLBI) *Evidence-Based Management of Sickle Cell Disease Expert Panel Report, 2014*—In adults and children with SCD and a vaso-occulsive crisis there is no specific guidance on opioid prescribing for outpatient use in terms of dosage and duration. "Rapidly initiate treatment with parenteral opioids in adults and children with a vaso-occlusive crisis associated with severe pain" (NHLBI, 2014; Yawn et al., 2014). SCAC (the Sickle Cell Advisory Committee) of GENES (The Genetic Network of New York, Puerto Rico, and the Virgin Islands) *Guidelines for the Treatment of People with Sickle Cell Disease*—"Mild to moderate pain is usually controlled with acetaminophen or NSAIDs. If pain persists or escalates, opioids should be added" (SCAC/GENES, 2002). New England Pediatric Sickle Cell Consortium *Management of Acute Pain in Pediatric Patients with Sickle Cell Disease (Vaso-Occlusive Episodes)*—"Consider discharge home from ED if pain is captured with minimal number of doses (≤2) of IV opioids and then controlled with oral medication" (New England Pediatric Sickle Cell Consortium, 2009).

continued

TABLE 5-3 Continued

	Criteria for Developing Clinical Practice Guidelines		
Indication	Prevalence of Medical Indication	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Sprains and strains, musculoskeletal	A meta-analysis of 144 studies found the incidence of ankle sprain is higher in females compared with males (13.6 versus 6.94 per 1,000 exposures), in children compared with adolescents (2.85 versus 1.94 per 1,000 exposures), and adolescents compared with adults (1.94 versus 0.72 per 1,000 exposures) (Doherty et al., 2014). Based on the U.S. National Electronic Injury Surveillance System of ED visits between 2002–2006, there were an estimated 3.1 million ankle sprains occurred among an at-risk population of 1.5 billion person-years for an incidence rate of 2.15/1,000 person-years (Waterman et al., 2010). In 2016, 3.0% of ED visits (145.6 million) were for sprains and strains of the neck, back, ankle or other areas (Schappert and Rui, 2019).	Between 2014–2015, opioid prescribing for opioid-naïve patients treated in EDs for ankle sprains varied at the state level from a low of 2.8% in North Dakota to 40.0% in Arkansas; median was 21.3% (Delgado et al., 2018). Between 2008–2016, of 454,813 opioid-naïve patients with an ankle sprain, 8.3% filled an opioid prescription within 7 days of diagnosis and among those who did so, 8.4% continued to use opioids more than 90 days later (Finney et al., 2019). In 2016, approximately 26–33% of ED patients with a sprain or strain received a discharge prescription for opioids (Schappert and Rui, 2019).	American Physical Therapy Association *Ankle Stability and Movement Coordination Impairments: Ankle Ligament Sprains–Clinical Practice Guidelines Linked to the International Classification of Functioning, Disability and Health from the Orthopaedic Section of the American Physical Therapy Association*—Does not mention opioids (Martin et al., 2013). Loveless and Fry *Pharmacologic Therapies in Musculoskeletal Conditions*—"For acute pain, short-acting opioids are recommended" (Finney et al., 2019).

TABLE 5-3 Continued

Indication	Criteria for Developing Clinical Practice Guidelines		
	Prevalence of Medical Indication	Evidence of Variation in Prescribing or Over- or Under-Prescribing	Selected Examples of Available Guidelines That Address Opioid Prescribing for Acute Pain for the Specific Indication
Tendonitis/bursitis	In 2014, among 176,607 patients visiting a primary care setting for an episode of acute pain, 13,371 patients had tendonitis/bursitis (Mundkur et al., 2019).	Among 13,371 patients with tendonitis/bursitis, 457 patients (3.4%) filled an opioid prescription within 7 days of initial visit, and 17.7% requested ≥1 refill (Mundkur et al., 2019).	American Physical Therapy Association *Achilles Pain, Stiffness, and Muscle Power Deficits: Midportion Achilles Tendinopathy Revision 2018—Clinical Practice Guidelines Linked to the International Classification of Functioning, Disability and Health from the Orthopaedic Section of the American Physical Therapy Association*—No mention of opioids (Martin et al., 2018b). Jones *Nonsurgical Management of Knee Pain in Adults*—Opioid analgesics should be used only if conservative pharmacotherapy is ineffective in patients who are not candidates for surgery (Jones et al., 2015). Javed *Elbow Pain: A Guide to Assessment and Management in Primary Care*—No mention of opioids (Javed et al., 2015). American College of Rheumatology *Tendinitis and Bursitis Fact Sheet*—No mention of opioids (Huston, 2019).

NOTE: CI=confidence interval; CPG=clinical practice guideline; ED=emergency department; MME=morphine milligram equivalent; NHANES=National Health and Nutrition Examination Survey; OME=oral morphine equivalent; SCD=sickle cell disease.

EMERGENCY DEPARTMENT CONSIDERATIONS

While there exists enough evidence for many acutely painful conditions, such as acute low back pain, to generate condition-specific guidelines on the use of opioids, the committee also recognizes the importance of having clinical setting–specific guidelines for pain management in patients after they are discharged from the ED (Chou et al., 2017; Qaseem et al., 2017). Pain is one of the most common reasons patients present to the ED, representing the primary symptom in 45% of visits (Chang et al., 2014). And the ED is the most appropriate care setting for the management of severe pain episodes, with primary care offices and outpatient clinics often triaging patients to the ED for acute management. Therefore, prompt, safe, and effective pain management is a core mission of clinical practice in the ED.

The NHAMCS for 2006–2010 indicated that opioids were prescribed for about 18.7% of all ED discharges (Kea et al., 2016). Kea et al. (2016) used NHAMCS data to assess ED discharge opioid prescribing practices for adults and children. During this period, there were 502.4 million ED discharges, in which opioids were prescribed for 94.0 million patients. Overall, opioid prescribing increased from 17.2 million discharges with opioids in 2006 to 20.2 million discharges with opioids in 2010. The rate of opioid prescriptions is 14.9% for ED visits and 2.8% for outpatient visits for adolescents and young adults (Hudgins et al., 2019).

The specialty of emergency medicine was among the first to promote specialty-specific pain management guidelines regarding opioid prescribing (ACEP, 2017; Cantrill et al., 2012; Motov et al., 2017). Today there are numerous national, state, and municipal CPGs and policy statements on acute pain management in the ED that include the use of opioids upon discharge from the ED (ACEP, 2017; Broida et al., 2017; Cantrill et al., 2012; Motov et al., 2017; NYCDOH, 2019).

When patients present to the ED with severe acute pain, ED clinicians carry out clinical assessments and diagnostic tests, seeking to identify the cause of the pain and to determine whether the patient should be admitted to the hospital or discharged. While in the ED, patients may receive treatment for acute pain and for the underlying cause of pain. Acute pain management in the ED is ideally patient-specific, pain syndrome–targeted, and based on appropriate pharmacologic and nonpharmacologic approaches (Motov et al., 2017). For example, some patients presenting with an acute shoulder dislocation may have their pain relieved with injection of lidocaine into the shoulder joint before relocating the shoulder, while others may require intravenous opioids to achieve adequate pain control prior to relocating the shoulder.

As in any clinical setting, the goals of managing patients with acute pain who are being discharged from the ED are to alleviate pain, restore function, and reduce the potential for adverse effects of medication. A common tenet in ED opioid prescribing guidelines is that given the known harms of opioid analgesia, ED clinicians should take every opportunity to use nonopioid and nonpharmacologic options to treat acute pain, especially on discharge, and to use opioid analgesics only when the benefits outweigh the risks (Strayer et al., 2017). For example, it has been found that among opioid-naïve patients with Medicaid insurance in Washington State who were prescribed opioids upon discharge from the ED, 13.7% went onto high-risk opioid use within 1 year, as compared with 3.2% among those who were not prescribed opioids (Meisel et al., 2019). Given that this finding is consistent across several studies in ED patients (Barnett et al., 2017; Hoppe et al., 2015a; Jeffery et al., 2018), in addition to the harms associated with diversion and misuse, a common recommendation for ED clinicians and others who treat acute pain is to keep opioid-naïve patients opioid-naïve when possible (Motov et al., 2017; Nelson et al., 2015).

The ability to assess a patient's response to treatments administered for pain in the ED allows for more individualized pain treatment than is possible in other outpatient settings. Thus, the patient's response to analgesic treatment in the ED can guide the choice of whether to prescribe opioids upon discharge as well as the dosage and duration. If opioids are determined to be necessary, the risks of opioids can be reduced by prescribing only immediate-release formulations at the lowest effective dose and for the shortest appropriate course (Strayer et al., 2017).

The time over which the acute pain is expected to resolve can guide the choice and duration of pain treatments. For example, a patient who presents with a dislocated shoulder that was relocated after intravenous analgesia is unlikely to have persistent severe pain, whereas a patient treated for long bone fracture is likely to require analgesia after discharge. For the majority of patients treated for acute pain in the ED, the pain improves or resolves within 6 days (Chapman et al., 2012); however, individual pain trajectories can vary widely (Daoust et al., 2019). Unlike the emerging literature documenting the average number of opioid pills used and left over after surgical procedures, there is a paucity of similar evidence for patients discharged from the ED. One study in a Canadian academic center ED found the median number of opioid pills consumed upon discharge was 7, but this varied from 3 pills for renal stones to 11 pills for fractures (Daoust et al., 2018). The authors concluded that opioid prescriptions from the ED for acute pain should be no more than a 3-day supply, with a maximum of 30 pills per prescription for patients with severe fracture pain (Daoust et al., 2018).

Finally, a key distinguishing aspect of emergency medicine practice is that ED clinicians do not have a longitudinal relationship with their patients. The standard of care in emergency medicine is to refer patients back to their primary care or outpatient longitudinal provider within 2–5 days for reassessment,

particularly if symptoms are not improving. Given that EDs serve as a safety net location of care for underserved patients without longitudinal care providers, discharge prescription dosing quantities need to account for the challenges that patients may face in obtaining adequate follow-up care. For patients who face barriers in obtaining timely outpatient follow-up, a recommendation of returning to the ED for reassessment if symptoms have not resolved or are worsening is prudent.

CONCLUSIONS

Thus, based on the information presented above, the committee finds that opioid prescribing for acute postoperative pain varies substantially by provider and hospital, including EDs. Furthermore, as shown in Tables 5-2 and 5-3, the committee finds that there is evidence that excessive opioids are prescribed for acute pain associated with both surgical procedures and some medical conditions. Consequently, the committee also finds that some opioid-naïve patients who receive opioids for acute postoperative pain and acute pain episode from medical conditions may develop new chronic opioid use.

Taken together, this body of evidence regarding variation in prescribing, excessive prescribing, and new prolonged use highlights the need to develop rigorous, evidence-based CPGs to direct opioid prescribing for the priority indications identified in Tables 5-2 and 5-3 that are aligned with actual patient use in order to minimize unwarranted variation and excess prescribing. Because different kinds of providers may be caring for patients during surgical and medical care and providing prescriptions, such as advanced practice providers, trainees, or surgeons, the opioid CPGs needs to meet the needs of these individual groups.

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6

Evaluating Clinical Practice Guidelines for Prescribing Opioids for Acute Pain

In Chapter 4 the committee proposed an analytic framework that professional societies, state and federal policy makers, health care systems, payers, and key stakeholders could consider when developing evidence-based clinical practice guidelines (CPGs) for prescribing opioids for acute pain associated with surgical or medical indications. The analytic framework is for opioid prescribing strategies only and is based on the assumption that a clinician has already determined that opioids are needed for acute pain management. However, this framework does not exclude the consideration and use of nonopioid options, both pharmacologic and nonpharmacologic, with or without opioid analgesics.

In Chapter 5 the committee identified priority surgical and medical indications for which CPGs should be developed or improved. These indications are associated with acute pain episodes and were prioritized according to the prevalence of the indication—which was used as a proxy for the indication's public health impact—and evidence that opioids play a role in acute pain management for these indications. In addition, the committee ascertained whether evidence-based CPGs were publicly available for any of the indications. If a CPG did not exist, other forms of guidance were considered.

In this chapter, the committee addresses its task of evaluating existing opioid prescribing guidelines for acute pain for selected indications from Chapter 5, against the analytic framework presented in Chapter 4. To do this, the committee identified seven indications—three surgical procedures and four medical conditions—that have public health impact, have some guidance and evidence regarding opioid prescribing, and were different in scope and context, to determine how the analytic framework might be applied to a range of indications that affect different populations. The three surgical procedures—cesarean and vaginal delivery, third molar (wisdom tooth) extractions, and total knee arthroplasty (TKA)—and the four medical conditions—renal stones, migraine headaches, low back pain, and sickle cell disease—differentially affect children, adolescents, adults, older populations, women of reproductive age, and minority populations. Evaluating any CPGs and other existing guidance chosen for each indication allowed the committee to identify opportunities for data optimization and research gaps for prescribing opioids.

The committee recognized that its task is predicated on the determination that opioids will be prescribed for acute pain for a given indication. However, in clinical practice the decision to use opioids

for acute pain often is made in the context of a comprehensive treatment plan tailored to an individual patient. Ideally, such a treatment plan considers the patient's health status (obtained from a patient interview and review of the patient's health record), including pre-existing conditions, comorbidities, prior reactions to opioids and other pharmaceuticals, treatment preferences, and the availability of and access to all recommended treatments. The comprehensive treatment plan for acute pain may include opioids alone or in conjunction with nonopioid and nonpharmacologic treatments prior to, concurrent with, or following the use of opioids. These other treatments may include heat, ice, physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), massage, and acupuncture, among others, depending on the specific indication and patient preferences. Patient education may also occur prior to prescribing opioids to ensure the patient understands his or her risks and benefits and is able to take the drug as prescribed. To acknowledge this need for a comprehensive treatment plan, the committee added the need for the clinician to consider the patient's medical history and to develop an acute pain management approach to its analytic framework, as shown in Figure 6-1. A CPG would consider evidence for all aspects of Figure 6-1 in order to provide an accurate and effective recommendation on opioid use and dosing for the treatment of acute pain for the indication. Should the opioids not provide the expected pain relief or if unexpected adverse effects occur, the clinician may reevaluate the patient to determine if the diagnosis is correct and if other treatments are warranted.

APPLYING THE ANALYTIC FRAMEWORK TO SELECTED SURGICAL INDICATIONS

The committee selected three surgical procedures on which to apply its analytic framework: cesarean and vaginal delivery, third molar (wisdom tooth) dental extractions, and TKA. These indications were

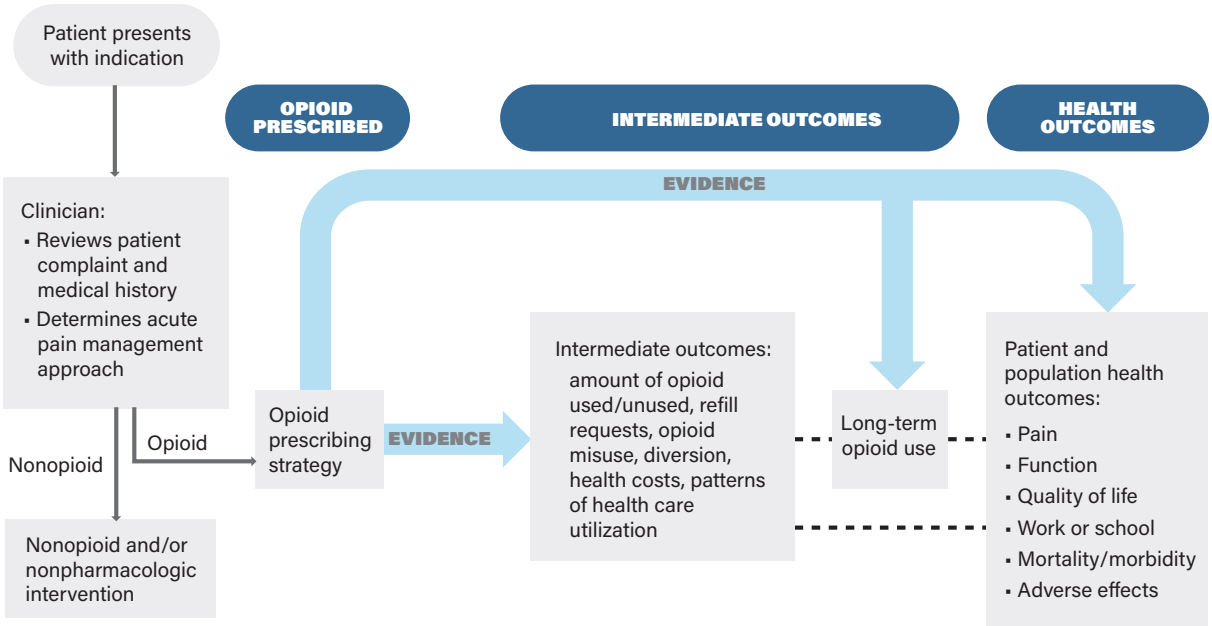

FIGURE 6-1 The committee's analytic framework for opioid prescribing in the context of a comprehensive acute pain management plan (left side of figure). As discussed in Chapter 4, the framework may be applied to assess the evidence on intermediate and health outcomes from various opioid prescribing strategies for acute pain for any of the surgical or medical indications listed in Chapter 5.

selected because they represent varied patient populations (e.g., women, adolescents, and older individuals) and are performed in different settings (e.g., inpatient or outpatient care). Moreover, across these procedures the majority of patients undergoing them are prescribed opioids for immediate postsurgical pain. Access to care and prescribed opioids may also vary for each of these procedures, depending on the patient's comorbidities, finances, health insurance, geography, and the care provider.

Cesarean and Vaginal Delivery

Childbirth is the most common reason for hospital admission and the most common procedure in the United States, with 3,855,500 births in 2017 (CDC, 2017a). Of these, approximately 32% (1,233,760) are cesarean deliveries and 68% are vaginal deliveries (2,621,740); of the latter, it is estimated that about 9% will have a severe perineal laceration (ACOG, 2016). In one study, opioids were prescribed for 86.7% of 3,288 women who delivered by cesarean delivery, with a median dose of 300 morphine milligram equivalents (MMEs) (interquartile range, 200–300); of the women who had a vaginal delivery, 30.4% were prescribed opioids at discharge with a median dose of 200 MMEs (interquartile range, 120–300) (Badreldin et al., 2018b). The amount of opioids prescribed for either delivery did not vary between women with a pain score of 0 of 10 and those with a pain score greater than 0 of 10 immediately prior to discharge. Bateman et al. (2017) found that among 720 women admitted to a hospital for cesarean delivery, 615 (85.4%) filled a discharge prescription for opioids. Mills et al. (2019) examined opioid prescribing data at discharge for women with uncomplicated vaginal delivery and found that almost 30% received opioids on the day of discharge; by contrast, Komatsu et al. (2018) found that fewer than 10% of women with vaginal deliveries used opioids after discharge. Compared with women in other countries, including Canada, Germany, and Sweden, patients in the United States were far more likely to receive opioid prescriptions after vaginal and cesarean delivery (Wong and Girard, 2018).

The committee chose childbirth as a priority procedure because of the prevalence of the procedure, the prevalence of opioid prescribing, the evidence of over-prescribing (Badreldin et al., 2018a), and the risk of persistent use of opioids after discharge (Peahl et al., 2019). The committee also notes that there is the potential for exposure of infants to opioids through breast milk (Ito, 2018). The committee applied its analytic framework to vaginal and cesarean deliveries to highlight how standardized methodology for CPG development may help identify the most effective opioid prescribing strategies along with the intermediate and health outcomes that may be associated with that prescribing.

Opioid Prescribing Guidelines

Although there is no evidence-based guidance that is labeled as a CPG and addresses opioid prescribing after vaginal or cesarean delivery, the American College of Obstetricians and Gynecologists' (ACOG's) *Committee Opinion on Postpartum Pain Management* makes a number of recommendations on the use of acetaminophen and NSAIDs, reserving opioid use for breakthrough pain (ACOG, 2018). The opinion recommends a shared decision-making model to optimize pain control and minimize unused opioid pills (ACOG, 2018).

The ACOG opinion paper (2018) provides a synopsis of the evidence that the authoring committee used to reach its recommendations, but this committee does not consider the opinion paper to be a CPG and recognizes that it is not intended to be. The ACOG committee collaborated with representatives of the American College of Nurse-Midwives and the American Academy of Family Physicians in developing its opinion paper. A conflict of interest statement is included.

In addition to the opinion paper, ACOG frequently publishes a number of practice bulletins, which are "evidence-based documents that summarize current information on techniques and clinical management issues."[1] To date, none of the bulletins apply to opioid prescribing at discharge after cesarean or vaginal delivery. The ACOG practice bulletins, unlike the committee opinions, address specific questions and have an in-depth presentation of supporting evidence for recommendations and conclusions. The recommendations are rated as Level A (good and consistent scientific evidence), Level B (limited or inconsistent scientific evidence), or Level C (primarily consensus and expert opinion). The practice bulletins also contain brief synopses of the literature search and discussions of how the subsequent articles were reviewed. For example, they were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force (USPSTF) (see ACOG, 2016). In contrast, the recommendations in the committee opinions are not rated, nor is there any information as to how the evidence was reviewed or obtained. In the sections below, this committee considers what evidence gaps need to be addressed to develop evidence-based CPGs for vaginal and cesarean deliveries.

Patient Populations

Patients who undergo cesarean or vaginal delivery may experience a variety of types and intensity of pain during the early postpartum period. The AGOC committee opinion paper distinguishes pain management for vaginal versus cesarean deliveries. Special consideration is given to women who experience postpartum pain while breastfeeding, have opioid use disorder, have chronic pain, or are using other medications or substances that may increase sedation. Clinicians are referred to an AGOC committee opinion on opioid agonist pharmacotherapy for women with opioid use disorder, the Centers for Disease Control and Prevention (CDC) CPG on chronic pain (Dowell et al., 2016), and the National Academies report on pain management, which has information for women with chronic pain (NASEM, 2017). Considerations regarding opioid prescribing for other pre-existing or comorbid conditions are not discussed, although the ACOG committee recognizes that the range of health and socioeconomic statuses among women who give birth may require opioid prescribing be modified to address an individual's physical and mental health, comorbidities, and home environment.

ACOG also has a committee opinion paper on *Opioid Use and Opioid Use Disorder in Pregnancy* (ACOG, 2017), which briefly discusses the use of opioids in postpartum women who used opioids during pregnancy, with a focus on breastfeeding. The opinion paper distinguishes among women who use opioids for medical reasons, who misuse opioids, and who have untreated opioid use disorder. ACOG also acknowledges that women who are ultra-rapid metabolizers of codeine may require close monitoring from their clinicians.

Most women who give birth are opioid naïve, having not filled an opioid prescription in the year prior to delivery, but they may have had varying degrees of opioid exposure prior to pregnancy. In addition, women may have various risk factors for prolonged opioid use following delivery, including pain disorders, mood disorders, and a history of substance use disorders (NIH, 2017; Osmundson et al., 2019; Sanmartin et al., 2019a,b).

Nonopioid Pain Management Strategies

The ACOG committee opinion paper recommends a stepwise nonopioid approach to postpartum pain management after vaginal or cesarean births, including both pharmacologic and nonpharmacologic

[1] See https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Bulletins-List (accessed August 28, 2019).

therapies. For vaginal births, the first step is acetaminophen or an NSAID. ACOG states that the most common sources of acute pain following vaginal delivery are breast engorgement, uterine contractions, and perineal laceration, which may be treated with nonpharmacologic modalities and mild anti-inflammatory analgesics.

ACOG does not comment on the use of either acetaminophen or NSAIDs as a first step for cesarean births.

Opioid Prescribing Strategies

The 2018 ACOG committee opinion paper states that if analgesics are insufficient for pain management following a vaginal birth, then milder short-acting opioids in combination with acetaminophen may be an effective second step for pain control while the woman is in the hospital (ACOG, 2018). It further states that using an NSAID and acetaminophen simultaneously on a set schedule with milder opioids, if needed, is preferred over opioid/acetaminophen combinations (two pills containing a maximum dose of 325 mg acetaminophen, administered every 4–6 hours) for vaginal births and cesarean deliveries. Overall, oral opioids should be reserved for breakthrough pain.

With regard to opioid use for postoperative pain following cesarean delivery, the ACOG committee opinion recommends the use of neuraxial opioids supplemented by oral acetaminophen, NSAIDs, opioids, and opioids in combination with either acetaminophen or an NSAID, but it does not specify if this includes pain control at discharge. Oral opioids should be reserved for breakthrough pain (ACOG, 2018). ACOG does not identify the number of pills or duration of opioid treatment to be prescribed at discharge, although it acknowledges that over-prescribing has been documented. It cautions that under-prescribing and inadequate pain control are also of concern and are best approached on an individualized basis. Finally, the ACOG opinion paper recommends that if an opioid is prescribed for postpartum pain, the duration should be limited to the "shortest reasonable course expected for treating acute pain" (p. e39).

The committee notes that a number of opioid prescribing strategies have been recommended for acute pain following vaginal or cesarean birth. However, some of the studies were published after the ACOG opinion paper and thus could not be included in it. Some of these studies are briefly reviewed to highlight the types of evidence that might be considered and graded for an updated ACOG opinion paper or for the development of a practice bulletin on postpartum pain.

Mills et al. (2019) developed expert panel consensus guidelines for opioid prescribing following uncomplicated vaginal births. Using a Delphi approach, the panel recommended that the lowest dose of immediate-release opioids should be used for the shortest period of time for acute pain; however, the type, dosage, and duration of opioid were not specified. A Johns Hopkins expert panel also concluded that opioids should not be routinely prescribed following an uncomplicated vaginal birth (Overton et al., 2018). Of note, these were not evidence-based guidelines and did not assess patient-reported outcomes.

With regard to cesarean delivery, the Johns Hopkins expert panel recommended that opioid-naïve patients be prescribed 0–10 pills of 5 mg oxycodone at discharge. Prabhu et al. (2017) found that in using a shared decision approach to opioid prescribing at discharge, women undergoing cesarean sections preferred to have 20 5 mg oxycodone pills prescribed rather than the standard prescription of 40 pills. The women in this study had a median of four unused pills at 2 weeks postdischarge and 90% (45 of 50) of them reported being satisfied or very satisfied with their outpatient pain management. These results are similar to those obtained by Bateman et al. (2017).

When an intervention to reduce prescribing following cesarean delivery was implemented (no preordered opioids while hospitalized), the use of opioids in the hospital was reduced from 68% to 45% by optimizing NSAID and acetaminophen use; at discharge only 40% received an opioid prescription,

compared with the preintervention rate of 91% (Holland et al., 2019). It is important to note that the discharge opioid prescription was based on inpatient use and shared decision making between the patient and prescriber in which patients could choose the number of pills they were prescribed up to a defined limit. A limitation of this study is that women were not interviewed regarding pain scores after discharge.

Intermediate Outcomes

There are robust data indicating that opioids are over-prescribed following childbirth. For example, approximately 75% of patients have unused opioids following cesarean delivery (Osmundson et al., 2017). On average, about 50% of opioids prescribed following cesarean delivery are unused, with 40 pills prescribed (various opioids) and 20 used (Bateman et al., 2017). Badreldin et al. (2018b) found that 45.7% of women after vaginal delivery and 18.5% of women after cesarean delivery who received an opioid prescription used 0 MME during the final hospital day. These data are in contrast to a small study by Osmundson et al. (2017) that found that 83% of women who had cesarean sections used opioids after discharge for a median of 8 days, and of the women who filled their prescriptions, 75% had unused pills (median per person 75 MME).

In a randomized controlled trial (RCT), Osmundson et al. (2018) found that individualized discharge opioid prescriptions based on an algorithm that correlated inpatient opioid use with postdischarge opioid use resulted in a greater than 50% reduction in the number of opioid pills prescribed at discharge after cesarean birth as compared with standard prescribing (average 14 pills versus 30 pills). Women in the individualized prescription group had 50% fewer unused pills and used only half the number of prescribed opioids than the standard group (8 pills versus 15 pills); patient-reported pain outcomes did not differ between the two groups. Prabhu et al. (2018) implemented a two-step strategy that decreased the usual discharge prescription following cesarean from 40 pills (5 mg oxycodone) to a maximum of 30 pills in the first patient education phase and to a maximum of 25 pills in the second phase, for an overall 35% reduction in the number of opioid pills prescribed, without an increase in refill requests (5–8%).

The ACOG opinion paper does not discuss intermediate outcomes such as unused pills, refill requests after discharge, or long-term opioid use. However, ACOG acknowledges that one of the reasons for making its recommendations is that 1 in 300 opioid-naïve patients exposed to opioids after cesarean birth will become a persistent opioid user (this estimate is taken from Bateman et al., 2016). Similar data are not given for vaginal births.

Health Outcomes

The ACOG opinion paper discusses health outcomes for the recommended analgesic therapies, including their effectiveness, possible adverse effects, and impacts on breastfeeding and comorbidities. In general, however, the health outcomes are not linked to specific opioid dosing. ACOG emphasizes that therapy should be individualized to each patient.

The committee notes that both short- and long-term health outcomes are concerns following discharge opioid prescribing. In a study of functional recovery following childbirth, pain- and opioid-free functional recovery occurred at a median of 20 days following vaginal delivery (opioid cessation occurred at a median of 0.5 days, with pain resolution at 15 days); on the other hand, following cesarean delivery, complete functional recovery did not occur until a median of 27 days (8 days for opioid cessation and 21 days for pain resolution) (Komatsu et al., 2018).

Of note, the risk of overdose in young children (median age 2 years) is markedly increased (odds ratio [OR]=2.41, 95% confidence interval [CI] 1.68–3.45) when the mother had received a prescription opioid in the preceding year (Finkelstein et al., 2017).[2]

Data Gaps and Research Needs

The committee identified several studies on specific opioid prescribing strategies used for vaginal or cesarean births and on the relationship of specific prescribing strategies with intermediate and patient outcomes. Areas where further research might be helpful for assessing long-term health outcomes include the use of opioids in patients with chronic opioid use, opioid use disorder, and indirect adverse effects on children in the home, including the effects on infants of mothers taking opioids while breastfeeding.

The committee found several studies of institution-specific quality improvement (QI) initiatives to reduce inappropriate postpartum opioid prescribing (Burgess et al., 2019; Holland et al., 2019; Prahbu et al., 2018). These studies documented a reduction in the opioid pills prescribed after the QI intervention and frequently, but not always, included data on patient-reported outcomes. Further information on opioid refills obtained outside the delivery hospital system and long-term outcomes would also be useful.

Third Molar Extraction

Opioid prescriptions for acute pain management after third molar extractions represent a significant proportion of opioid prescribing by dentists. It is estimated that 7–10 million third molar extractions are performed annually, making this procedure one of the most common procedures in dentistry associated with opioids for acute pain management (Friedman, 2007).

Baker et al. (2016) found that among a national sample of Medicaid patients (mean age 24.9 years) who underwent dental extraction between 2000 and 2010, 42% had filled an opioid prescription within 7 days of the procedure; hydrocodone was the most commonly prescribed opioid (78%). Early exposure to opioids in this population may increase the risk of persistent use and possible abuse, particularly in young females (Schroeder et al., 2019).

Dentists have traditionally managed postoperative pain after tooth extraction using NSAIDs, acetaminophen, and short-duration opioids (33–140 MMEs) (Gupta et al., 2018). The overall short-acting opioid prescribing rate of dentists since 2005 has been in the range of 12–18.5% (median of 16.5%) for all dental procedures according to nationwide studies (Gupta et al., 2018; Levy et al., 2015; Moore et al., 2006). In a study of opioid prescribing practices by dentists in South Carolina, however, the percentage of all initial opioid prescriptions after dental procedures was 45% (McCauley et al., 2016). Thus, regional variations exist for opioid prescribing practices by dentists.

There is evidence that a filled opioid prescription after third molar extractions increases the risk of persistent opioid use among opioid-naïve users aged 16–30 (Harbaugh et al., 2018). Furthermore, using 13- to 15-year-olds as a basis of comparison, the likelihood of persistent opioid use increased with increasing age (OR=1.39, 95% CI 1.01–1.91 for 16- to 18-year-olds; OR=2.13, 95% CI 1.55–2.92 for 19- to 24-year-olds; and OR=2.85, 95% CI 1.87–4.34 for 25- to 30-year-olds).

The committee chose third molar extraction as a priority surgical procedure for which a CPG might be developed because of the patient populations that are affected (e.g., adolescents and young adults), the high prevalence of the procedure, and the data that document the efficacy of nonopioid pain management strategies for this procedure.

[2] This text has been revised since prepublication release.

Opioid Prescribing Guidelines

Currently, there are no evidence-based CPGs that specifically address opioid prescribing for the management of acute pain after third molar extractions. Both the American Dental Association (ADA) and the American Association for Oral and Maxillofacial Surgeons (AAOMS) provide some guidance for opioid prescribing, but they both defer the specific prescribing details to the best clinical judgment of the dental practitioner. The ADA Center for Evidence-Based Dentistry does not have any guidelines for pain control. However, the ADA website[3] contains two statements that pertain directly to opioids: the 2018 *Policy on Opioid Prescribing* and the 2016 *Statement on the Use of Opioids in the Treatment of Dental Pain*. The statement recommends "consideration of nonsteroidal anti-inflammatory analgesics as the first-line therapy for acute pain management" but does not specify the type, release duration, or dosage of opioids to be considered for breakthrough pain (ADA, 2016). The statement also recommends that dentists follow and continually review CDC and state licensing board recommendations for safe opioid prescribing, as well as register with and make use of prescription drug monitoring programs. The policy states that "ADA supports statutory limits on opioid dosage and duration of no more than 7 days for the treatment of acute pain, consistent with CDC evidence-based guidelines" (ADA, 2018). There is no supporting documentation for any of these recommendations, nor is there a description on how the recommendations were derived. The committee did not consider these statements to meet the criteria for CPGs described by the 2011 Institute of Medicine (IOM) report *Clinical Practice Guidelines We Can Trust*. The committee notes that in 2015 ADA also developed *The ADA Practical Guide to Substance Use Disorders and Safe Prescribing*, and it has a number of webinars that provide more detailed information on specific aspects of opioid use in dentistry. Because the webinars are not CPGs, the committee did not consider them for this report.

The AAOMS white paper *Opioid Prescribing: Acute and Postoperative Pain Management* has a similar recommendation regarding NSAIDs as a "first-line analgesic therapy" and also states, "When indicated for acute breakthrough pain, consider short-acting opioid analgesics. If opioid analgesics are considered, start with the lowest possible effective dose and the shortest duration possible" (AAOMS, 2017).

The Center for Opioid Research and Education (CORE) Dental Opioid Guidelines, developed by a multidisciplinary consortium of dentists, periodontists, oral and maxillofacial surgeons, endodontists, and patients, used a modified Delphi approach to make recommendations for a stepped approach to treating acute pain in opioid-naïve patients undergoing any of 14 common dental procedures (CORE, 2018). For third molar extractions, CORE recommends that pain treatment begin with 1 g acetaminophen or 400 mg ibuprofen every 8 hours and, if needed, the maximum amount of opioids prescribed may be 15 5 mg oxycodone pills at discharge, based on the clinician's assessment of the patient's pain needs.

The committee selected ADA's guidance on opioid prescribing as the basis for its evaluation of the analytic and evidence frameworks presented in Chapter 4 because ADA has a large membership whose members prescribe opioids and it has been engaged in the opioid overdose epidemic for several years.

Patient Populations

The ADA website contains little information on the patient populations that may be prescribed opioids. The 2016 ADA *Statement on the Use of Opioids in the Treatment of Dental Pain* recommends, "When considering prescribing opioids, dentists should conduct a medical and dental history to determine current medications, potential drug interactions, and history of substance abuse." *The ADA Practical Guide to*

[3] See https://www.ada.org/en/advocacy/current-policies/substance-use-disorders (accessed August 28, 2019).

Substance Use Disorders and Safe Prescribing has "techniques for managing dental pain for those who may be at risk for substance dependence" (ADA, 2015). However, the committee notes that this is a relatively small population compared with the number of people who have third molar extractions. In addition, the webinars on the ADA website have information regarding opioid prescribing in adolescents.

The lack of information on opioid prescribing for various patient populations undergoing third molar extractions is of concern because the patient population is predominantly between the ages of 15 and 25 years and those patients are typically opioid naïve.

Nonopioid Pain Management Strategies

The ADA *Statement on the Use of Opioids in the Treatment of Dental Pain* states that "dentists should consider nonsteroidal anti-inflammatory analgesics as the first-line therapy for acute pain management" and "recognize multimodal pain strategies for management for acute postoperative pain as a means for sparing the need for opioid analgesics" (ADA, 2016).

The committee notes that there is an abundance of strong evidence that NSAID/acetaminophen combination therapy is more efficacious than opioid therapy for acute pain after third molar extractions, with fewer side effects (Moore et al., 2018). Acute pain management after third molar extractions has been shown to respond to nonopioid medications, such as NSAIDs (e.g., ibuprofen or diclofenac) combined with acetaminophen, for pain relief equivalent to short-acting opioids. However, NSAIDs may be contraindicated in some patients, such as those with kidney or liver diseases. These nonopioids may be combined with physical modalities (ice/heat) and behavioral management for pain management (AAPD, 2018; Abdeshahi et al., 2013). Patients with breakthrough pain should be re-evaluated for other causes of pain such as infection or alveolar osteitis (dry socket). Excluding these causes, consideration of a short-acting opioid for a short duration may be indicated.

The committee recognizes that the adoption and incorporation of these alternatives to opioid prescribing in dentistry has been slow. The result has been dentists prescribing excess amounts of opioids after third molar extraction, resulting in some that are unconsumed (Mutlu et al., 2013), which allows for potential opioid diversion (Ashrafioun et al., 2014).

Opioid Prescribing Strategies

The 2018 ADA *Policy on Opioid Prescribing* states that "ADA supports statutory limits on opioid dosage and duration of no more than 7 days for the treatment of acute pain, consistent with CDC evidence-based guidelines." Further information on why ADA supports this recommendation is not provided.

The committee finds that there is a paucity of prescribing strategies for the opioid management of acute pain after third molar extraction. Because third molar extraction pain typically lasts 3 to 5 days after the procedure, a prescription for 7 days of opioids may result in over-prescribing. Although short-acting, short-duration strategies for opioid dosing have been successful (Moore and Hersh, 2013), data on the specific dosing levels and duration have not been adequately evaluated.

Intermediate Outcomes

Neither the ADA *Policy on Opioid Prescribing* nor the ADA *Statement on the Use of Opioids in the Treatment of Dental Pain* provides information on any intermediate outcomes associated with opioid prescribing, such as the amount of opioids used for acute pain management.

A recent prospective study reported that patients used less than half of the prescribed opioids to manage their pain and reported more side effects when using opioids than when using nonopioid alternative medications (Maughan et al., 2016). However, most studies have been retrospective examinations of combined insurance and prescription databases on such outcome measures as the type of opioid and the strength and duration of prescriptions. The committee notes that one limitation to studies that use these data is that not all patients who have third molar extractions are represented because some patients may not have insurance that covers the procedure.

Health Outcomes

Neither the ADA *Policy on Opioid Prescribing* nor the ADA *Statement on the Use of Opioids in the Treatment of Dental Pain* provides information on any health outcomes associated with opioid prescribing for acute pain following third molar extraction.

The committee notes that the need for the long-term management of postextraction pain using opioids is minimal, a fact that is reflected in the lack of literature evaluating long-term health outcomes. Other sequalae subsequent to the extraction that may cause pain and require management include chronic infection and nerve injury. These sequalae require nonopioid, alternative approaches that are appropriate for managing these conditions (Bouloux et al., 2007).

Data Gaps and Research Needs

Opioids are commonly prescribed for third molar extractions, but the appropriate prescribing strategies for the typically young, opioid-naïve patients have not been studied. Additional research is needed to establish appropriate dosages because there is evidence that patients have different responses to pain due to, for example, their sex, age, history of substance use disorder, or history of persistent pain, and thus may require higher or lower doses to successfully manage their pain.

Health outcomes after short-term opioid use for third molar extraction pain have received minimal attention and represent another evidence gap. Further research is needed to identify the effects of opioids on such outcomes as the quality of life, the risk of substance use disorder, chronic opioid use, function, and mortality. This information would be useful in the acute pain management discussions between the prescriber and patient prior to third molar extractions.

Total Knee Arthroplasty

TKA, or knee replacement, is commonly performed in the United States for the treatment of symptomatic osteoarthritis, and opioids are typically prescribed for postoperative pain (Murphy and Helmick, 2012). The committee chose TKA as a priority surgical procedure for which a CPG might be developed because TKA is a relatively common procedure, procedure rates have increased in recent years, postoperative opioid prescribing is standard practice, opioid-naïve patients at the time of surgery are at risk for chronic opioid use, and a substantial proportion of patients undergoing TKA have current or recent opioid exposure.

In 2014 there were more than 752,900 knee arthroplasty procedures, making it the third most frequent operating room procedure (rate of 236.1 per 100,000 people) (McDermott et al., 2017). Moreover, given the aging population, TKA rates are expected to increase. Sloan et al. (2018) projected that the number of TKAs performed in the United States will grow by 85% to 1.26 million procedures by 2030, on the basis of 2000–2014 data from the Agency for Healthcare Research and Quality (AHRQ) and the National Inpatient Sample developed for the Healthcare Cost and Utilization Project.

Most patients undergoing TKA receive opioids for postoperative pain control. An analysis of health insurance administrative claims found that 72.0% of opioid-naïve patients undergoing TKA between 2007 and 2016 filled an opioid prescription, while 84.2% of sporadic opioid users and 95.9% of chronic opioid users filled an opioid prescription after surgery (Cook et al., 2019). Opioid prescribing varies considerably following TKA (Holte et al., 2019; Kahlenberg et al., 2019; Sabatino et al., 2018). For example, Sabatino et al. (2018) found that patients who underwent TKA were prescribed a median of 90 5 mg oxycodone equivalent opioid pills, with the number ranging from 10 to 200 pills. The extent to which opioids are under- or over-prescribed following TKA is unclear. Approximately 67% of patients received at least 1 refill, for a total mean number of pills prescribed of 176.4±108.0 (range, 10–480); the mean number of unused pills at 90 days was 29 (Sabatino et al. 2018).

The trajectory of opioid use following TKA varies by patient factors and prior opioid exposure. In a study of insurance claims (Bedard et al., 2017), the percentage of patients filling an opioid prescription fell from 69.3% patients in the first month after TKA to 24.9% at 3 months and to 14.9–16.3% at 6–12 months after surgery. Among opioid-naïve patients, 10.2%, 4.0%, and 3.3% were using opioids at 3, 6, and 12 months after surgery. In contrast, patients who were using opioids at the time of surgery were more likely to continue to fill prescriptions in the months following surgery, with 50.4%, 38.3%, and 33.2%, doing so at 3, 6, and 12 months after surgery. In addition, patients younger than 50 years and female patients were more likely to continue to fill prescriptions. Patients with anxiety, depression, low back pain, myalgia, and drug or alcohol dependence or who used tobacco were also more likely to continue filling prescriptions. Finally, Goesling et al. (2016) noted that among opioid-naïve patients, continued opioid use at 6 months was correlated with greater overall body pain, greater joint pain, and catastrophizing reported by patients on the day of surgery.

Importantly, there is growing evidence that opioid prescribing after TKA can be reduced without compromising pain control. In an RCT, 304 arthroplasty patients received either 30 or 90 5 mg oxycodone pills at discharge. The lower dose arm had fewer unused pills at 30 days postoperatively, with no difference in pain score. There was also no difference in patient-reported outcomes at 6 weeks. At 90 days, the lower dose arm also had lower mean MMEs prescribed, with no difference in the number of MMEs consumed (Hannon et al., 2019). Two single-institution QI initiatives also suggested that opioids are currently over-prescribed after TKA. Holte et al. (2019) found that implementing a strict opioid prescribing guideline after TKA resulted in a decline in the initial opioid prescription, the number of refills, and the total postoperative dose. Kahlenberg et al. (2019) reported that after implementation of a new opioid prescribing guideline, which set a limit of 70 pills after total joint replacement, the mean number of pills prescribed decreased from 91±26.6 pills to 65±16.3 pills, and the number of postoperative telephone encounters also decreased (the authors noted that most postoperative calls are typically to nurse practitioners for prescription refills). Neither of these QI reports contacted patients postoperatively about pain or unused pills or opioids prescribed beyond the surgical providers.

Opioid Prescribing Guidelines

In 2015 the American Academy of Orthopaedic Surgeons (AAOS) published *Surgical Management of Osteoarthritis of the Knee: Evidence-Based Clinical Practice Guideline*, which was endorsed by several professional societies, including the American Association of Hip and Knee Surgeons. This CPG does not specifically mention opioid use for acute pain after TKA, but it does make strong recommendations for the inpatient use of the pain management techniques of peri-articular local anesthetic infiltration, peri-articular nerve blockade, and neuraxial anesthesia to decrease opioid use when performing orthopedic procedures (Weber et al., 2016). The CPG contains both inclusion and exclusion criteria

for the evidence base, and it follows a pre-established protocol for CPG development that tracks closely with the procedures recommended in the 2011 IOM report *Clinical Practice Guidelines We Can Trust* and the rationale of the USPSTF for making expert opinion-based recommendations.

Additionally, in 2015 AAOS also published an information statement supporting the standardization of opioid prescription protocols and policies in all settings to control and limit opioid prescription use and dose (AAOS, 2015). The information statement recommends the following strategies for ensuring safe opioid prescribing:

- Establish ranges for acceptable amounts and durations of opioids to treat postprocedural pain, tailored to the intensity of the procedure (small, moderate, and large procedures);
- Avoid prescriptions from multiple providers, and coordinate prescribing with primary care or the usual prescribers for patients currently on opioids;
- Review prescription drug monitoring programs prior to prescribing;
- Avoid prescriptions for the treatment of chronic pain; and
- Have a strict limit of opioid prescription size that is expected to be appropriate to the pain.

Patient Populations

As discussed previously, approximately 30% of patients undergoing TKA are exposed to opioids at the time of surgery, and opioid requirements for opioid-exposed patients are often higher than for opioid-naïve patients (Bedard et al., 2017; Cook et al., 2019; Goesling et al., 2016). In addition, mental health conditions, overall body and surgical site pain, medical comorbidities, and tobacco and other substance use are correlated with greater opioid use following surgery (Bedard et al., 2017; Cook et al., 2019; Goesling et al., 2016). The AAOS CPG provides evidence and recommendations on risk factors that may affect postoperative outcomes, including the rates of complications, revision, function, and patient-reported outcomes. These risk factors include body mass index, comorbidities (e.g., diabetes, liver disease, chronic pain), compliance with preoperative therapy, and depression and anxiety. However, the CPG examines only chronic pain as a risk factor for outcomes following surgery and does not specifically address preoperative opioid use.

Nonopioid Pain Management Strategies

The AAOS CPG for TKA identifies peripheral nerve blockage and peri-articular local anesthetic infiltration as best practices to enhance postoperative pain control, and it cites the supporting evidence and specifies its quality. For example, the CPG notes strong evidence (defined as two or more high-quality studies) to support the use of peripheral nerve block versus parenteral opioids alone to reduce postoperative opioid consumption, minimize opioid-related side effects, improve postoperative range of motion, and enhance patient-reported outcomes in the immediate postoperative period. Similarly, there is strong evidence to support the use of peri-articular infiltration of local anesthesia for postoperative pain control, as it was superior to a placebo in enhancing postoperative function, reducing opioid use, improving patient-reported pain, and increasing patient-reported satisfaction following TKA.

Concerning pharmacologic opioid alternatives, a recent systematic review indicates that NSAIDs offer similar relief to opioids for knee osteoarthritis (Smith et al., 2016). One meta-analysis examined the use of alternative therapies after TKA to reduce pain and opioid use (Tedesco et al., 2017). In that study, electrotherapy and acupuncture after TKA were associated with reduced and delayed opioid consumption, but continuous passive motion, preoperative exercise, and cryotherapy were not.

Opioid Prescribing Strategies

Opioids are routinely prescribed following TKA (Bedard et al., 2017). As noted earlier, numerous studies have examined opioid dosing for TKA and provide an evidence base to be considered when creating guidelines for postoperative opioid prescribing following TKA. The AAOS CPG does not specifically address opioid prescribing following TKA, although it does consider opioid use and pain control as outcomes by which other best practices should be examined. Although enhancing pain control and reducing opioid use are identified as optimal outcomes, the best practices in opioid prescribing are not described (e.g., use, dosing, and timing of opioid alternatives alongside opioid analgesics and the identification of patients at risk for poor pain- and opioid-related outcomes), and no information is given on the type of opioid, dosing, or duration that should be followed in the postoperative period.

The AAOS statements highlight the importance of clinician–patient discussions about pain—including the use of a pain relief toolkit to facilitate those discussions—and behavioral interventions to address "depression, post-traumatic stress disorder, and ineffective coping strategies" (AAOS, 2015), but no further guidance on the latter intervention is given. This information is not included in the AAOS CPG.

Intermediate Outcomes

The committee identified several studies that have examined the intermediate outcomes following opioid use, including the amount of opioids prescribed and refilled and health care use for follow-up pain management such as telephone calls, emergency visits, and rehospitalizations. In addition to the previously mentioned 2019 studies by Hannon et al., Holt et al., Huang and Copp, and Kahlenberg et al., all of which found that opioids were over-prescribed after TKA surgery, long-term opioid use of up to 1 year following TKA surgery has also been described (Bedard et al., 2017). These studies typically obtained data from databases such as electronic medical records and administrative databases from health insurers. The results include, for example, the finding that opioid refills declined in the months following TKA, from 69% in the first month after surgery to 15–16% at 6–12 months after surgery (Bedard et al., 2017). Overall, approximately 8% of opioid-naïve patients continue to use opioids at 6 months, compared with roughly 53% of opioid-exposed patients (Goesling, 2016). Importantly, patients with preoperative opioid exposure also reported less pain relief following TKA (Smith et al., 2017). Approximately 60% of patients require refills of opioids, and the refill rates are lower among patients with optimal pain control in the hospital prior to discharge (Wilke et al., 2019).

The AAOS CPG does not address any intermediate outcomes for opioid dosing, although it does state that the use of its recommended pain management techniques may reduce opioid use.

Health Outcomes

Many of the studies described previously did not analyze patient-reported health outcomes such as pain reduction, function, or return to work or other activities. A few studies, however, have interviewed patients at varying times after surgery to ascertain pain status (Huang and Copp, 2019).

Studies using only administrative data do not capture patient-reported outcomes such as pain, opioid use, and satisfaction; however, recent studies have examined the effect of reductions in opioid prescribing on patient outcomes following TKA. For example, in an RCT Hannon et al. (2019) compared 30 or 90 pills of oxycodone following TKA and total hip arthroplasty and found that smaller opioid prescriptions reduced the number of unused pills but made no difference in patient-reported pain (Hannon et al., 2019). Similarly, Huang and Copp (2019) examined 51 consecutive patients undergoing TKA and noted over-prescribing by 34% compared with the amount used and the pain reported.

The 2015 AAOS CPG does address best practices specific to postoperative outcomes including complications, readmissions, revision rates, functional outcomes, and patient-reported outcomes, which indirectly address pain and opioid use following surgery. The guidelines include such statements as "Moderate evidence supports that patients with select chronic pain conditions have less improvement in patient reported outcomes with TKA." However, the AAOS CPG has no recommendations on opioid prescribing at discharge. It does have strong recommendations regarding perioperative interventions and immediate postoperative outcomes. For example, the CPG states, "Strong evidence supports that peripheral nerve blockade for TKA decreases postoperative pain and opioid requirements." Four studies are cited that compared opioids with nerve block in terms of patient outcomes; the assessments were made on the first postoperative day, and long-term opioid use and pain outcomes were not well characterized.

Data Gaps and Research Needs

The committee considered the available evidence and guidelines, including expert testimony at the committee's public sessions, and identified the following evidence gaps. First, it has been suggested that there is a need for multicenter prospective studies using common definitions of key terms and data elements and a standardization of multimodal perioperative pain programs (David Jevsevar, Dartmouth, personal communication, July 9, 2019). In addition, it will be critical to ensure appropriate and uniform risk adjustment for baseline predictor variables (e.g., prior opioid exposure, medical comorbidities, mental health conditions, and social determinants of health). Jevsevar also suggested the greater use of quality improvement registries and longitudinal databases of large vertically integrated health systems that have high retention rates. Furthermore, Jevsevar called attention to patients who have additional types of pain and to polypharmacy in frail elderly patients as well as to the importance of the settings of care, including site of surgery and discharge location. The committee concurs with these ideas and notes that other research gaps include risk stratification for complex pain and interventions to treat these individuals.

The committee also identified evidence gaps in intermediate outcomes (e.g., opioid use disorder) and patient-reported health outcomes (e.g., function, quality of life). As noted above, the committee found evidence gaps regarding nonpharmacological pain treatments, including patient education and behavioral therapy (Tedesco et al., 2017). In light of the high prevalence of opioid use among patients before TKA, the committee found evidence gaps regarding co-management strategies among orthopedic surgeons, pain specialists, and primary care clinicians, particularly for opioid-exposed patients. Addiction medicine specialists may also be important to include for patients with opioid use or substance use disorders who are undergoing TKA surgery. Notably, the majority of opioid prescribers for patients with knee arthritis undergoing TKA may not be orthopedic surgeons; primary care and internal medicine physicians have been found to be the highest opioid prescribers before and after total joint arthroplasty (Namba et al., 2018). Moreover, nurse practitioners and physician assistants in orthopedic departments may also prescribe opioids postoperatively. This suggests that a collaborative effort to develop guidelines for opioid prescribing after TKA that includes input from these other prescribers would enhance the reach and impact of such a guideline and improve prescribing practices.

APPLYING THE ANALYTIC FRAMEWORK TO SELECTED MEDICAL INDICATIONS

The acute pain associated with surgical procedures is usually assumed to be time limited as the patient recovers from the surgery or procedure. However, the acute pain associated with many medical

conditions is much more variable and depends on the nature of the indication. For example, the acute pain associated with renal stones is typically limited to the time required for the stone to move from the kidney or ureter to outside the body. Once the renal stones are eliminated, the acute pain is expected to subside. The acute pain resulting from a sprained joint, broken bone, or strained muscle may also be expected to ease once the joint, bone, or muscle heals. Preventing acute pain from becoming chronic is an important consideration in pain management.

The committee chose four medical indications that are known to have acute pain episodes with which to assess its analytic framework for opioid prescribing: renal stones, migraine headache, low back pain, and sickle cell disease. Assessing these indications allowed the committee to determine whether the guidance available for each indication addressed issues such as acute versus chronic pain, specific opioid prescribing, other treatment modalities, population variations, and intermediate or health outcomes. Renal stones generally occur in a mature population and often result in emergency department (ED) visits. Migraine headaches may occur in both children and adults and are frequently treated in EDs, but may also be treated in primary care and specialty clinics. Acute low back pain is relatively common, can be debilitating, and may have a variety of causes that are difficult to diagnose. Sickle cell disease may also occur in both adults and children and affects predominantly black and, to a lesser extent, Hispanic populations. These indications provided a range of medical conditions and varying levels of clinician guidance to help the committee determine whether its analytic framework is broadly applicable to medical conditions.

Renal Stones

Renal stones are a common cause of acute pain. The terms renal stones, kidney stones, renal colic, and nephrolithiasis are used interchangeably to refer to the underlying obstruction in the urinary system that causes the pain. Stones may be composed of a variety of compounds, most commonly calcium oxalate and calcium phosphate (Türk et al., 2016). Based on data from the 2007–2010 National Health and Nutrition Examination Survey (NHANES) of the U.S. population, the overall prevalence of kidney stones was calculated to be 8.8% (95% CI 8.1–9.5), 10.6% (95% CI 9.4–11.9) among men, and 7.1% (95% CI 6.4–7.8) among women. Compared with whites, blacks and Hispanics were less likely to report a renal stone (OR=0.37, 95% CI 0.28–0.49 and OR=0.60, 95% CI 0.49–0.73, respectively) (Scales et al., 2012). Almost 1 in 11 people in the United States experience renal stones at some point in their lives (Pearle et al., 2014).

Opioids are frequently prescribed for acute pain caused by renal stones. In the 2016 National Hospital Ambulatory Medical Care Survey (NHAMCS), opioids were found to have been prescribed for more than 300,000 ED visits for patients diagnosed with renal calculus. Renal stones accounted for 2.1% of all ED visits at which opioids were prescribed at discharge (Schappert and Rui, 2019). In the 2010 NHAMCS, the diagnosis with the highest proportion of discharge opioid prescriptions was nephrolithiasis, with 62.1% of patients receiving an opioid prescription (Kea et al., 2016). In primary care clinics, Mundkur et al. (2018) found that renal stones were the eighth leading cause of opioid prescribing for acute pain, with 15.3% of patients receiving a prescription for opioids at the initial visit.

Opioid Prescribing Guidelines

Practice guidelines exist for acute pain caused by renal stones. In particular, the European Association of Urology (EAU) issued comprehensive evidence-based guidelines for the diagnosis and management of renal stones in 2019.[4] The committee also found that EAU developed its evidence-based guidelines for

[4] See https://uroweb.org/guideline/urolithiasis (accessed June 27, 2019).

renal colic using a methodology that is consistent with the analytic and evidence frameworks described in Chapter 4. The EAU evidence summary for the management of renal colic declares, "Non-steroidal anti-inflammatory drugs are very effective in treating renal colic and are superior to opioids (Section 3.4.1.1), with the level of evidence rated as 1b." The EAU guidelines made a strong recommendation to "offer a non-steroidal anti-inflammatory as the first drug of choice (Section 3.4.1.1)." The guidelines made a weak recommendation to "offer opiates … as a second choice," with specific mentions of hydromorphone, pentazocine, or tramadol. EAU also issued guidelines on medical therapy to expel stones and on active stone removal through shock wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy.

Nevertheless, Europe and the United States differ with regard to clinical practice, the scale of opioid misuse, and attitudes toward pain relief with opioids. Moreover, the committee noted that several RCTs described in the EAU guideline for acute renal colic were carried out in other countries (e.g., Bansal et al., 2016; Ener et al., 2009) where clinical practice and cultural expectations regarding pain and relief of pain may differ from those in the United States. Thus, the committee did not consider the EAU guidelines to be appropriate for assessing its framework for opioid prescribing for acute pain from renal stones. A systematic review of studies on the prevention of renal stones in adults was performed for the American College of Physicians CPG, but it does not deal with treatment of pain caused by renal stones (Fink et al., 2013).

The American Urological Association (AUA) issued evidence-based guidelines for the medical management of renal stones in 2014 (Perle et al., 2014) and also for the surgical management of renal stones.[5] The committee found that these guidelines were based on a systematic review of evidence and that the methodology of the evidence review and standards for guideline recommendations were consistent with the committee's guideline development process and the evidence framework. However, these AUA guidelines did not consider the management of acute pain due to renal colic or the specific use of opioids. Moreover, the literature review for the medical management guideline was only through 2011, and key studies considered by the EUA guidelines were published after this date. Still, these guidelines demonstrate that AUA has a standardized process in place for developing evidence-based CPGs.

Patient Populations

Renal stones are more common in certain U.S. populations (Scales et al., 2012; Shoag et al., 2015). Between 1994 and 2010 the prevalence of renal stones increased and in 2010 was found to be 10.6% in men (95% CI 9.4–11.9) and 7.1% in women (95% CI 6.4–7.8). Blacks and Hispanics have a lower prevalence of renal stones than whites, although the prevalence among blacks rose by more than 150% during this period (Scales et al., 2012). The prevalence of renal stones has also risen among children and adolescents, and stones are more frequent among girls than boys, unlike the situation in adults (Shoag et al., 2015). Renal stones are more common among people with obesity, diabetes, and metabolic syndrome; the increase in these conditions may be driving the increased prevalence of stones (Scales et al., 2012). Renal stones are also more common in people with a lower intake of fluids and dietary calcium.

Both of the AUA guidelines address the occurrence of renal stones in adults and children. Both guidelines also offer recommendations on the diagnosis and treatment of renal stones based on the stone type and size. No other patient considerations are given in the guidelines.

[5] See https://www.auanet.org/guidelines/kidney-stones-surgical-management-guideline (accessed June 27, 2019).

Nonopioid Pain Management Strategies

Because the management of acute pain is not considered in the AUA guidelines for the medical and surgical management of renal stones, and because consideration of other management strategies is outside the scope of the committee's task, the committee was unable to assess the use of opioids for acute pain from renal stones. Nevertheless, the committee found numerous studies that have assessed the pharmacologic treatment of pain due to renal stones. Some of this evidence is briefly described below. These studies might provide a foundation for assessing pain management in future guidelines. The committee also notes, as described previously, that the EAU recommends NSAIDs to treat renal stones.

There is considerable evidence to support the use of nonopioid pharmacotherapies for renal stones. Pathan et al. (2018) carried out a systematic review and meta-analysis of 36 RCTs on the efficacy of NSAIDs, opioids, and paracetamol (acetaminophen) in the treatment of acute renal colic. In these trials, pharmaceuticals were generally administered intravenously or intramuscularly with a pain assessment conducted about 30 minutes later. The analysis concluded that, compared with opioids, NSAIDs had a marginal benefit for initial pain reduction at 30 minutes, required fewer rescue treatments, and had lower vomiting rates. NSAIDs and paracetamol did not differ in pain relief at 30 minutes, but NSAIDs required fewer rescue treatments. The review concluded that NSAIDs should be the preferred analgesic option for patients presenting to the ED with renal stones, despite heterogeneity among the included studies and the overall quality of evidence. The committee notes that the clinical outcome in these trials was pain relief at 30 minutes and not at discharge. The trials did not study patient-reported outcomes such as longer-term pain relief, function, ability to work, or quality of life.

The 2018 review by Pathan et al. included a large 2016 placebo-controlled RCT whose active arms were 75 mg of intramuscular diclofenac, 0.1 mg/kg of intravenous morphine, and 1 gram of paracetamol (Pathan et al., 2016). In the primary endpoint, reduction of initial pain by 50% or more at 30 minutes, diclofenac was statistically superior to morphine, and paracetamol approached statistical superiority over morphine. Diclofenac had a statistically significant lower frequency of rescue analgesia and persistent pain than the other arms. The study concluded that "intramuscular non-steroidal anti-inflammatory drugs can be safely used as the first-line treatment and offer the fastest, most effective, and sustained relief from renal colic presentations in the emergency setting" (p. 2000). The study has been criticized for using a fixed single dose of morphine rather than titrating the dose (Riou and Aubrun, 2016). Of note, the study was conducted in Qatar, and the median age of participants was 34.7 years. Hence, the committee notes that the findings may not be generalizable to the population of the United States. Pathan et al. (2018) reached conclusions similar to those in a 2005 Cochrane review (Holdgate and Pollock, 2005).

In addition, there is some evidence suggesting that nonpharmacological pain modalities may be effective in relieving acute pain from renal colic, and thus, might be part of a nonopioid and nonpharmacologic approach that could reduce the need for opioids (e.g., Ayan et al., 2013; Beltaief et al., 2018; Kaynar et al., 2015).

Opioid Prescribing Strategies

The AUA evidence-based guidelines for the medical management of renal stones (Perle et al., 2014) do not address acute pain management, with or without opioids.

The EAU guidelines for renal stones recommend clinicians "offer opiates (hydromorphine, pentazocine, or tramadol) as a second choice"; this recommendation is based on weak evidence. There is a further recommendation that pethidine be avoided for patients with renal stones. No further opioid dosing information is provided.

An important limitation of the clinical trials analyzed in evidence-based reviews is that opioids were generally used at a single fixed parenteral dose in EDs. This prescribing protocol is outside the scope of this report, which is focused on opioid prescribing for outpatients or at discharge.

Intermediate Outcomes

The AUA evidence-based guidelines for the medical management of renal stones (Perle et al., 2014) do not address intermediate outcomes that may be associated with prescribing opioids for acute pain management. The committee found no studies that address intermediate outcomes of opioids prescribed for acute renal colic, such as the number of pills used and the number left over or relief of pain several days after treatment.

Health Outcomes

The AUA evidence-based guidelines for the medical management of renal stones (Perle et al., 2014) do not address the health outcomes that may be associated with prescribing opioids for acute pain from renal stones. The committee found no reports of functional status, quality of life, or the ability to work or go to school after treatment with opioids or nonopioid interventions for acute pain from renal stones.

Shoag et al. (2019) analyzed NHANES data and found that patients reporting a greater number of passed stones were also more likely to report current opioid use. This relationship persisted when smoking and arthritis, which are known to be associated with opioid use, were taken into account in a multivariable analysis. The authors acknowledged the limitations of the cross-section survey design and their inability to verify the patient-reported history of renal stones.

Data Gaps and Research Needs

Single-dose NSAIDs are effective for the short-term relief of acute pain due to renal colic and are marginally more effective than parenteral opioids in fixed doses, and they have fewer adverse effects. Evidence is lacking from RCTs regarding prescribing opioids or other medications for renal colic. Additional research on QI initiatives to reduce opioid over-prescribing for acute pain from renal colic that assess pain relief several days after discharge from the ED, the dosage of unused opioid pills, or the need for opioid refills would also be helpful (e.g., Motov et al., 2018).

Migraine Headache

Migraine headaches can cause severe pain with significant disability. They are one of the top five pain conditions among 18–44-year-olds that are treated in EDs according to a 2011 national survey (Weiss et al., 2014),[6] although the 2016 National Hospital Ambulatory Care Survey did not include migraine headaches among the top 20 conditions for which opioids are prescribed in the ED (Schappert and Rui, 2019). Headaches are one of the top 10 conditions treated with opioids in primary care settings (Mundkur et al., 2018), but this categorization also included general headaches.

Migraine headache is common among people presenting for care for acute pain. The 1-year period prevalence of migraines is about 18% in women and 6% in men, with the prevalence peaking between the ages of 25 and 55 years (AHS, 2019). Migraines also occur in children and adolescents, with their prevalence increasing with age (1–3% in 3- to 7-year-olds, 4–11% in 7- to 11-year-olds, and 8–23% by

[6] This text has been revised since prepublication release.

age 15 years) (Oskoui et al., 2019). In adults, migraines may be either episodic (fewer than 15 migraine or headache days in 1 month) or chronic (at least 15 monthly headache days with at least 8 monthly migraine days) (AHS, 2019). Diagnostic criteria for pediatric migraines include at least five headaches over the past year that lasted 2–72 hours when untreated, with requirements for additional features and associated symptoms (Oskoui et al., 2019).

A majority of migraine sufferers (approximately 52%) are seen in primary care settings, while 17% are treated in the ED (Burch et al., 2015). Acute migraine causes 1.2 million visits to EDs annually (Orr et al., 2016). The management of migraine headaches consists of preventive approaches using a wide variety of nonopioid medications and interventions (Silberstein et al., 2012).

The committee selected migraines for its assessment of its analytic framework because they are common, opioids are prescribed for them, and the diagnosis is sufficiently narrow to enable research to fill in data gaps. Despite the fact that opioids are not recommended for migraines as first-line therapy, they are frequently prescribed to patients presenting in emergency outpatient settings. Furthermore, headaches are one of the key conditions associated with a large rise in opioid prescribing in EDs (Dodson et al., 2018; Minen et al., 2018).

Opioid Prescribing Guidelines

Guidelines and supporting documentation for the pharmacological management of acute migraines have been published and updated by the American Headache Society (AHS)[7] and the American Academy of Neurology (AAN) (Marmura et al., 2015). These guidelines promote the initial prescribing of a variety of nonnarcotic medications prior to prescribing opioids such as butorphanol for regular use. However, the adoption of these guidelines has been variable in clinical practice.

The 2000 report *Practice Parameter: Evidence-Based Guidelines for Migraine Headache (an Evidence-Based Review): Report of the Quality Standards Subcommittee of the American Academy of Neurology* (Silberstein, 2000) was based on four evidence-based reviews performed by Duke University and sponsored by AHRQ. Two of the reviews covered self-administered drug treatment for migraine and parenteral drug treatment for acute migraine. A technical review by AHRQ contains details of the methodology and grading of the evidence considered for the guideline; the technical review considered both the effect on headache pain and the tolerability of self-administered drug treatments for acute migraine headache compared to placebo, alternative drug treatments, and non-drug therapies in controlled trials (Gray, 1999). Efficacy and adverse events are also reported.

In 2018, the AHS Position Statement on Integrating New Migraine Treatments into Clinical Practice was released. Marmura et al. (2015) reviewed the evidence on which the AHS document and the Silberstein (2000) conclusions are based. Marmura et al. (2015) outlined their review process and how they rated the evidence. Their paper also states that the authors' approach is "consistent" with that in the 2011 IOM report *Clinical Practice Guidelines We Can Trust*.

The AHS paper builds on AAN's CPG (Silberstein, 2000). For the AAN guideline, seven organizations formed the U.S. Headache Consortium, which developed the document. Members of the consortium were identified, levels of evidence were graded, and the strength and quality of the evidence, scientific effect measures, and clinical impression of effect were defined. According to the AHS (2019, p. 3) position statement, "Input was … elicited from multiple stakeholders, including health insurance providers, employers, pharmacy benefit service companies, device manufacturers, pharmaceutical and

[7] See https://americanheadachesociety.org/resources/guidelines/guidelines-position-statements-evidence-assessments-and-consensus-opinions (accessed August 28, 2019).

biotechnology companies, patients, patient advocates, and experts in headache medicine from North America and Europe."

It is important to note that this guideline is specific to adults with migraines. However, a study using 2007–2008 commercial claims data of adolescents aged 13–17 years with two or more claims for a headache found that nearly half (46%) of the adolescents had received an opioid prescription (DeVries et al., 2014). On the date of the prescription, 24% had been diagnosed with a migraine, and nearly one-third (29%) received three or more opioid prescriptions during the study's observation period. The *Practice Guideline Update Summary: Acute Treatment of Migraine in Children and Adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society* (Oskoui et al., 2019) recommends both preventive medications and nonopioid analgesics as first-line management in children. However, the guideline also notes that treatment strategies will depend on the exact diagnosis as well as patient characteristics. The pediatric guidelines for migraine state, "There is no evidence to support the use of opioids in children with migraine" (Oskoui et al., 2019, p. 10).

A Canadian primary care group adapted six high-quality guidelines published through 2011 to develop a CPG for the management of adult headaches, *Primary Care Management of Headache in Adults, Clinical Practice Guideline, September 2016, 2nd Edition* (see Becker et al., 2015). In that guideline, opioids are listed as a fourth-line treatment for migraines.

Patient Populations

The 2019 AHS position statement notes that "the severity, frequency, and characteristics of migraine vary among persons and, often, within individuals over time, and symptom profiles or biomarkers that predict efficacy and side effects for individuals have not yet been identified" (p. 2). The statement goes on to say that treatment plans need to be individualized based on the patient's preferences and health status, the course of the patient's migraine episodes (e.g., presence, type, and severity of associated symptoms and attack-related disability), contraindications (e.g., cardiovascular disease), and the use of concomitant medications (AHS, 2019). The position statement also encourages clinicians to pay specific attention to women who may be or wish to become pregnant, as preventive medications may be teratogenic.

Nonopioid Pain Management Strategies

Silberstein (2000) and the AHS (2019) conclude that prevention is critical to migraine management and that both pharmacological and nonpharmacological methods may be effective in preventing migraines. Silberstein (2000) states that nonpharmacologic treatment may be used prior to or during a migraine. Nonpharmacologic treatments include behavioral treatments, categorized as relaxation, biofeedback therapy, and cognitive–behavioral training, and physical treatments such as acupuncture, cervical manipulation, and mobilization. The AHS (2019) recommends the use of NSAIDs or nonopioid analgesics and an acetaminophen and caffeinated analgesic combination for adult patients with mild to moderate migraine episodes and recommends triptans or dihydroergotamine for moderate to severe episodes. For pediatric migraine, the AHS (2019) recommends the use of nonopioid analgesics, such as ibuprofen, as an initial treatment option. The AHS emphasizes the importance of preventive pharmacologic therapies including triptans, but notes that they are underused, are not always effective and may have side effects. The AHS (2019) notes that only 3–13% of patients with migraine use preventive treatments and estimates that approximately 40% of patients with episodic migraine and almost all of those with chronic migraine could benefit from preventive treatment.

Opioid Prescribing Strategies

Overall, there is little evidence about the best opioid prescribing strategies other than that opioid use should be avoided when possible. A gap in the literature needed for CPG development is an indication of which prescribing strategies minimize adverse outcomes if and when opioids are used. Silberstein (2000) grades the pharmacologic treatments for acute migraine as follows:

- butorphanol nasal spray (Grade A quality evidence, strong scientific and clinical effect, frequent adverse effects; consensus role: moderate to severe migraine; rescue therapy, limit use); and
- oral combinations of acetaminophen and codeine (Grade A quality evidence, less strong scientific and clinical effect, occasional adverse effects; consensus role: moderate to severe migraine; rescue therapy, limit use).

The recommended adult prescribing strategies in Silberstein (2000) include the following:

- Butorphanol nasal spray is a treatment option for some patients with migraine (Grade A); and
- Butorphanol may be considered when other medications cannot be used or as a rescue medication when significant sedation would not jeopardize the patient (Grade C).

The AHS (2019) specifically indicates that while there is established evidence that the opioid butorphanol is effective for migraine, it is not recommended for use (p. 10); there is no citation to explain the reason for this recommendation. Codeine/acetaminophen and tramadol/acetaminophen combinations are listed as probably effective for migraines with auras; specific references for the ratings are not given. Marmura et al. (2015) reviewed studies of tramadol alone and of tramadol in combination with acetaminophen and found both to be effective in reducing migraine pain, but not eliminating pain. Pringsheim et al. (2016) stated that in migraine patients for whom initial treatments for acute pain relief have failed,

> opioids or acetaminophen in combination with codeine or tramadol can be considered, provided they are used infrequently. While butorphanol nasal spray has received a Level A recommendation, and codeine/acetaminophen and tramadol/acetaminophen have received Level B recommendations in the AHS acute treatment guidelines, these medications are not recommended for routine use because of concerns about dependence, addiction, and the development of medication overuse headache. (p. 1198)

According to the AHS (2019), for acute pediatric migraine treatment there is evidence to support the efficacy of ibuprofen and acetaminophen for children and adolescents and of triptans primarily for adolescents. Additional recommendations focus on early treatment for acute migraine episodes and counseling on lifestyle factors that can exacerbate migraine, including avoiding triggers and medication overuse.

Intermediate Outcomes

Intermediate outcomes were not addressed in either Silberstein (2000) or the AHS (2019).

Health Outcomes

All of the studies included in Silberstein (2000) or the AHS (2019) focused on pain relief and in some cases on adverse effects from the use of opioids such as butorphanol. No other health outcomes or harms were reported.

Data Gaps and Research Needs

There is a paucity of information on the long-term health outcomes associated with the prescribing of opioids for migraine headaches. Lipton et al. (2019) recently examined unmet treatment needs of acute migraine patients using oral medications, including opioids, and found that 96% of respondents to the Migraine in American Symptoms and Treatment survey had one or more unmet treatment needs, such as inadequate freedom of pain after 2 hours (48%), recurrence within 24 hours of initial relief (38%), or delay of treatment secondary to fear of side effects (21%). Among those reporting unmet needs, 8.1% had opioid or barbiturate overuse (defined as use during 10 or more days per month). This suggests the need for further evaluation of opioid misuse and of opioid's lack of effectiveness for migraines.

The AHS position paper (2019) stated that symptom profiles or biomarkers that predict efficacy and side effects for individuals have not yet been identified (AHS, 2019). The committee concludes that such research would be helpful in refining and individualizing the use of opioids and nonpharmacologic treatments for migraines.

Low Back Pain

Low back pain is a common diagnosis in EDs (Kea et al., 2016; Schappert and Rui, 2019) and primary care clinics (Ashman et al., 2018; Mundkur et al., 2018). In 2010, low back pain was the leading indicator for years lived with disability (U.S. Burden of Disease Collaborators, 2013). As shown in Chapter 5, Table 5-3, there is evidence that opioids are frequently prescribed for low back pain in EDs (Rui et al., 2016) and primary care (Deyo et al., 2011; Mundkur et al., 2018). Opioid prescribing practices for back pain are not uniform and may vary by geographic region (Webster et al., 2009), patient age (Pierce et al., 2019), and clinician adherence to prescribing guidelines (Hanley et al., 2017). There are many pharmacologic and nonpharmacologic treatment options for acute pain associated with low back pain, and data show that opioid prescribing for acute low back pain is significantly associated with long-term continued opioid use (Sanger et al., 2019).

In this section, the committee focuses on adults with acute low back pain episodes for whom pain management may include opioids. Given its frequency and impact, the management of low back pain has been the subject of extensive research, systematic reviews, and CPGs.

Opioid Prescribing Guidelines

Numerous organizations have developed guidance documents for the management of low back pain. The most recent is the 2017 CPG on acute, subacute, and chronic low back pain from the American College of Physicians (discussed in more detail below). Other organizations that have developed guidance for the treatment of back pain include the U.S. Department of Veterans Affairs/U.S. Department of Defense (VA/DoD, 2014), the Institute for Clinical Systems Improvement (ICSI, 2018), Kaiser Permanente (2017), the American Physical Therapy Association (Delitto et al., 2012), the American College of Occupational and Environmental Medicine (Hegmann et al., 2014), and the joint CPG from the American Pain Society and the American College of Physicians (Chou and Huffman, 2007). International organizations with multiple member countries, including Australia, Brazil, Canada, the Netherlands, and the United Kingdom, as well as countries in Africa, have also developed CPGs for the diagnosis and treatment of low back pain (Oliveira et al., 2018).

The committee focused on a recent, comprehensive evidence-based CPG on low back pain, which was published in 2017 as *Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain:*

A Clinical Practice Guideline from the American College of Physicians (ACP CPG) (Qaseem et al., 2017), along with a supporting systematic review (Chou et al., 2017b), to evaluate the evidence within the context of the analytic framework described in Chapter 4. The 2017 guideline is a partial update of the 2007 American College of Physicians guideline addressing management of acute, subacute, and chronic low back pain; acute back pain was defined as lasting less than 4 weeks. The 2017 guideline also described radicular low back pain as resulting in lower extremity pain, paresthesia, or weakness from nerve root impingement.

The ACP CPG is an evidence-based guideline that meets many of the criteria for a CPG discussed in Chapter 4. It identifies the authors of the guideline, the methodology for the ACP CPG development process, and the grading system used for evidence review. The CPG was based on "two background evidence reviews and a systematic review sponsored by the Agency for Healthcare Research and Quality" (Chou et al., 2016, 2017a,b). The strength of recommendations ("strong" or "weak") and the quality of evidence ("high," "moderate," or "low") were graded according to an established system (Qaseem et al., 2010). The CPG and the underlying evidence reviews were subjected to peer review and published in a medical journal (Qaseem et al., 2017). Disclosures of conflicting interests for the CPG authors are available online. Key questions are provided in an appendix along with the literature search strategy. Thus, the committee finds that the ACP CPG development process aligns with the process described in Chapter 4 and in the 2011 IOM report *Clinical Practice Guidelines We Can Trust*.

Patient Populations

The ACP CPG states, "The target audience for this guideline includes all clinicians, and the target patient population includes adults with acute, subacute, or chronic low back pain" (Qaseem et al., 2017, p. 1). For example, patients could have radicular or nonradicular low back pain or symptomatic spinal stenosis.

Nonopioid Pain Management Strategies

The CPG addresses numerous pharmacologic and nonpharmacologic interventions for low back pain. Studies that were assessed include those comparing different interventions versus placebo or against one another. The ACP CPG recommends that acute pain management of low back pain begin with nonpharmacologic treatments because they are effective at improving pain and function and have fewer side effects than pharmacologic therapy (Qaseem et al., 2017). The CPG notes that most acute pain is self-limited, improving "over time regardless of treatment"; thus, treatment is mainly for short-term symptomatic relief. Superficial heat is recommended, based on moderate-quality evidence. Other recommended interventions, albeit with low-quality evidence, are massage, acupuncture, and spinal manipulation. If pharmacologic interventions are used, the ACP CPG recommends NSAIDs or skeletal muscle relaxants, based on moderate-quality evidence indicating improved function and pain versus placebo.

Opioid Prescribing Strategies

The ACP CPG concluded that there is insufficient evidence to determine the effect of opioids versus placebos for acute low back pain. Based on one RCT included in the ACP systematic review, naproxen with a combination of oxycodone and acetaminophen did not improve acute low back pain or functional outcomes at 1-week follow-up compared with naproxen plus placebo, naproxen plus acetaminophen, or

naproxen plus cyclobenzaprine (Friedman et al., 2015). Moreover, the group randomized to oxycodone/acetaminophen had a higher rate of adverse effects than the group randomized to placebo, including drowsiness, dizziness, and nausea or vomiting. The number of harms with opioid use was approximately equal to the number of benefits. Of note, this trial excluded patients with radicular symptoms. Therefore, the ACP CPG does not list opioids as a recommended pharmacologic treatment for acute low back pain, and opioid prescribing strategies in persons with acute low back pain are not addressed. The ACP CPG recommends that opioids only be considered as a treatment option in patients who fail first-line therapies such as NSAIDs, duloxetine, or tramadol, and in patients for whom benefits are likely to outweigh risks. (Note: Tramadol is an opioid.)

There is some evidence that opioids continue to be frequently prescribed for acute low back pain and that there is substantial variation among providers. In an urban ED, for instance, clinicians' opioid prescribing rates varied from 12.0% to 78.2% (Hoppe et al., 2017).

Intermediate Outcomes

The ACP CPG focuses on the clinical benefits and harms of opioids and does not address intermediate outcomes such as opioid over-prescribing, the number of pills prescribed, or refills. However, in the RCT of a combination of oxycodone and acetaminophen versus placebo in addition to naproxen, Friedman et al. (2015) found that 31% of patients in the oxycodone/acetaminophen arm took the medication only once or not at all within 1 week, as compared with 23% of the placebo group, suggesting that there may be leftover opioid pills. However, these intermediate outcomes do not need to be addressed in the CPG for acute low back pain as there is a strong recommendation, based on moderate-quality evidence, that pharmacologic treatment with NSAIDs or skeletal muscle relaxants is preferred to the use of opioids.

Health Outcomes

As noted previously, an RCT found that naproxen plus oxycodone/acetaminophen did not improve functional outcomes compared with naproxen plus placebo or naproxen plus cyclobenzaprine (Friedman et al., 2015). This RCT was cited in the ACP CPG for back pain. There are also observational studies on the use of opioids for low back pain such as the studies by Franklin et al. (2008) and Webster et al. (2007), but they are not cited in either the ACP CPG or in the AHRQ review (Chou et al., 2017a) on which the CPG is based.

There are some studies showing that early use of opioids for acute low back pain is associated with worse outcomes regarding worker's compensation for disability (Franklin et al., 2008; Webster et al., 2007). An earlier review found that "opioids do not seem to expedite return to work in injured workers or improve functional outcomes of acute back pain in primary care" (Deyo et al., 2015, p. 1). However, a more recent systematic review of studies that examined possible adverse outcomes from the use of opioids for acute low back pain, Sanger et al. (2019) found that initial opioid prescribing was associated with long-term opioid use (an intermediate outcome), but not associated with the duration of unemployment as a result of back pain.

Data Gaps and Research Needs

The committee finds that opioid dosing may not be the primary issue regarding the development or revision of a CPG for acute low back pain because of the lack of evidence that opioids are more effective for this indication. Therefore, more research is needed to determine whether opioids are effective for

treating acute low back pain and which patients may be more responsive to opioids and under what circumstances (e.g., in case of a lack of response to other treatments, particularly NSAIDs).

The one RCT by Friedman et al. (2015) and the earlier studies showing long-term adverse outcomes in workers call into question the assumption of most health care providers, particularly ED clinicians, that early administration of opioids is effective for treating acute low back pain. Thus, it should be a priority to develop evidence to more closely examine the short- and long-term effectiveness of opioids for low back pain with respect to several patient-centered outcomes. Evidence can be gathered from RCTs or from cohort studies; the latter may be particularly useful for studying longer-term outcomes such as disability and opioid misuse or the development of chronic back pain. Such studies might also identify populations where opioids are more or less effective, such as those with different pain severity, back pain with or without the presence of radiculopathy, or prior response to opioids. The committee notes that if there is evidence that opioids are effective in some populations with acute low back pain, then additional research that focuses on optimal prescribing strategies in those populations would be warranted, but until effectiveness is established, there will be no advantage in comparing different doses.

Earlier studies on the long-term adverse effects of early opioid prescribing among workers with low back pain, including the Franklin et al. (2008) and Webster et al. (2007) studies described earlier and new studies by Cifuentes et al. (2010) and Furlan and Carnide (2010), found that opioid use was associated with more adverse effects (e.g., more disability at 1 year, higher medical costs, an increased risk of surgery, and long-term opioid use), but these studies did not find the results to be definitive and recommended more research. However, these studies were carried out before the peak of opioid morbidity and mortality in the United States and before the appreciation of serious public health risks linked to excessive opioid prescribing by clinicians. The ACP evidence review concluded that there is moderate evidence from a well-designed RCT that nonpharmacologic treatments are as effective for acute low back pain as opioids. Other pharmacologic treatments have fewer adverse effects than opioids for patients and no serious and widespread public health risks. In light of the ongoing opioid overdose epidemic and the availability of effective and safer drugs, the committee does not prioritize further studies to assess the long-term harms of opioids in patients with low back pain.

The committee recognizes that opioids are currently prescribed for acute back pain, thus, it is reasonable to assess how current prescribing practices—duration and dose—for opioids might affect both intermediate and clinical outcomes, including long-term opioid use, the number of unused opioid pills, and long-term health outcomes. Such studies are most easily conducted as retrospective or prospective observational studies or as QI initiatives conducted within a health care institution or clinical department. In Chapter 7, the committee discusses the methodological challenges with such observational or QI studies.

Sickle Cell Disease

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy that affects both children and adults. It is characterized by such phenotypic features as vaso-occlusive crisis (VOC); nociceptive, ischemic, and inflammatory responses; and acute and chronic pain; and it is multi-focal. According to CDC (2017b) there are about 100,000 cases of SCD in the United States, and about 60% are adults (Brousseau et al., 2010). SCD occurs in about 1 out of every 365 black or African-American births and 1 out of every 16,300 Hispanic-American births; about 1 in 13 black or African-American babies is born with the sickle cell trait (CDC, 2017b).

There are about 700,000 ED visits and nearly as many hospital admissions annually for SCD crisis, and 22% of the deaths in patients with SCD occur during acute painful crisis. People with SCD who have higher rates of pain also have increased mortality rates (NHLBI, 2014). Although most children with SCD live to be adults, in general their lifespans are shortened by 20–30 years (NHLBI, 2014).

The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) is a public–private partnership with the U.S. Food and Drug Administration (FDA), the American Pain Society (APS), and the American Academy of Pain Medicine (AAPM). This collaboration developed the ACTTION–APS–AAPM Pain Taxonomy (AAAPT) (Field et al., 2019). The AAAPT defines acute SCD pain (crisis) as lasting for at least 2 hours, and having had its onset within the past 10 days; must exhibit at least one physical sign (i.e., tenderness to palpation, pain on movement, or decreased range of motion); is not explained by a SCD complication, with or without a painful comorbidity; and occurs with or without chronic SCD pain. Acute SCD pain occurs more frequently than chronic SCD pain.

Opioid Prescribing Guidelines

CPGs have been developed to treat pain associated with SCD. In 1999 the APS produced the *Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease* (Benjamin et al., 1999). This was the first comprehensive evidence-based guideline to address treatment of the pain of SCD. In 2014 the National Heart, Lung, and Blood Institute (NHLBI) produced the *Evidence-Based Management of Sickle Cell Disease Expert Panel Report, 2014*, which may be considered an evidence-based CPG that addresses the comprehensive management of SCD, including acute pain episodes (e.g., VOC) and other acute symptoms of the disease such as renal failure, hepatobiliary complications, and fever (see also Adams-Graves and Bronte-Jordan, 2016; Yawn et al., 2014). The CPG offers guidance to primary care and emergency medicine providers for the appropriate care of adults, infants, children, and adolescents with SCD, including the management of acute complications. Public comments from outside stakeholders, including medical societies, patient advocacy organizations, and industry were considered in developing the report, and the report was endorsed by a number of professional organizations involved in SCD management.

The process for developing the CPG is explained at some length and follows the recommendations of the IOM (2011) and USPSTF. Specifically, the scope of the expert panel was defined, key questions were developed, and a literature search was conducted using a population–intervention or exposure–comparator–outcome–setting methodology (see NHLBI, 2014, Exhibit 2). The CPG is based on 549 studies, including RCTs. The report authors note that only a few RCTs and large prospective cohort studies have been conducted in the management of SCD. Where evidence was lacking or inadequate, the panel relied on member expertise to provide practical guidance (NHLBI, 2014). Evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. The framework was also used to rate the strength of the recommendations, although the panel modified GRADE to include a moderate strength/evidence category. Systematic reviews and CPGs from other organizations were reviewed and included if they were applicable to the SCD population, even if they did not deal directly with patients with SCD, such as guidelines on pain management for other pain-related indications. Panel recommendations for managing acute pain in SCD were adapted from other professional societies, specifically the APS's 1999 guideline for managing the pain of SCD (Benjamin et al., 1999). With regard to managing VOC acute pain, the panel stated, "Many specific recommendations for acute VOC management are included in this section that address treatment beyond what is listed in

the Key Question. The expert panel felt it was important to include current practices that have not yet been validated by evidence, but are currently being used" (p. 32).

Patient Populations

The NHLBI CPG recommendations are intended to be for all settings where patients present with VOC. The manifestation and diagnosis of VOC are discussed, including genotype variations in presentation. The CPG notes that there are no biomarkers or imaging studies to assess VOC pain severity. The NHBLI CPG states, "Emergency Severity Index (ESI) Version 4 triage system, which is used by more than half of emergency departments in the United States, suggests that persons with SCD be triaged as ESI level 2, a very high priority, and rapid placement be facilitated" (p. 32). Pain management both in the ED and at home are considered.

The acute pain management algorithm in the NHLBI report is applicable to any health care setting where a patient with SCD and with VOC may present for care. The recommendations for treating VOC are applicable to both adults and children. Treatment considerations for VOC in subpopulations of patients (e.g., elderly patients or patients with comorbidities) are not included.

Nonopioid Pain Management Strategies

The NHBLI CPG states that the primary management of VOC is analgesia, typically with opioids. Concurrent therapies, including heat, hydration, and nonpharmacologic therapy, are recommended to help with pain control. Antihistamines may also be used to treat itching secondary to opioid administration in the acute VOC management phase.

Opioid Prescribing Strategies

The NHBLI CPG (2014) does provide some recommendations on opioid dosing, but they are almost exclusively meant for an ED or hospital inpatient setting. It recommends treating severe VOC pain with parenteral opioids. The dose is to be "based on total daily short-acting opioid dose currently being taken at home to manage the VOC" (p. 34). The duration of dosing is dependent on the severity of the pain, and, if opioids are used, then they should be administered every 15–30 minutes until the patient reports that his or her pain is under control. Doses may be maintained or escalated by 25% until the pain is controlled, and pain relief and side effects should be assessed after each opioid dose.

For patients taking long-acting opioids at home for chronic pain, the guideline recommends that the decision to continue long-acting opioids in the setting of acute pain be made on an individual basis. In most circumstances, clinicians are advised to continue oral long-acting opioids to avoid a break in coverage and prevent withdrawal. The CPG does not provide specifics on the opioids that may be most effective and for whom, nor does it provide explicit information on the dose or duration of prescribing. The CPG does state that meperidine is not to be used, unless it is the only effective opioid for an individual patient.

The NHLBI CPG makes several recommendations regarding opioid dosing during the time the patient presents for care in the ED or a hospital setting that is outside the scope of this report. However, the CPG makes the following recommendations on the use of opioids for patients at discharge from either setting:

- At discharge, evaluate inpatient analgesic requirements, wean parenteral opioids prior to conversion to oral opioids, and adjust home dose of long- and short-acting opioid prescriptions to prevent opioid withdrawal after discharge. (Consensus–Panel Expertise)
- In adults and children with SCD and a VOC, do not use meperidine unless it is the only effective opioid for an individual patient. (Consensus–Adapted)

Intermediate Outcomes

Because acute pain in SCD is typically episodic and recurrent, the committee recognizes that it may be difficult to apply the analytic framework and assess the impact of different opioid prescribing strategies on long-term health outcomes. However, it may be possible to assess the effect of different prescribing strategies on intermediate outcomes such as the number of refills requested and the number of pills used and unused. The committee acknowledges that such information may not be indicative of opioid use because some patients with SCD may also be taking opioids for chronic SCD pain and not all VOCs are managed in the ED. Nevertheless, it may be possible to link opioid prescribing strategies to refill requests and fewer adverse effects or other health outcomes.

The NHBLI report does not discuss any intermediate effects from the use of opioids for acute pain for VOC.

Health Outcomes

The NHBLI CPG cites evidence (two RCTs and two observational studies) that opioids are effective for treating acute VOC pain (Benjamin et al., 1999; NHLBI, 2014). However, it also bases the recommendation on "indirect, high-quality evidence from populations without SCD" (p. 33). In particular, the NHLBI report cites the 2009 APS review of studies on chronic noncancer pain (Chou et al., 2009).

The NHBLI CPG does not present evidence that opioids may cause adverse health effects in either children or adults, although it does recommend adjusting the home dose of opioids to prevent withdrawal after discharge. There are no studies linking opioid doses to pain relief outside of the hospital.

Data Gaps and Research Needs

SCD is a relatively rare disease, which makes it difficult to study, particularly using RCTs to assess the effectiveness of various opioid prescribing strategies. A priority research need is to further research the management of VOCs in patients on chronic opioids or with chronic pain, possibly in combination with an opioid use disorder. Such research would require a multidisciplinary QI initiative.

The NHLBI report indicates that more research is needed to "better describe the clinical course of the occurrence and treatment results of all the acute and chronic complications of SCD; comparative effectiveness studies to provide clear outcomes on best approaches to SCD and its complications" (p. 93).

Because SCD affects largely communities of color, there is also a need for any prescribing guideline to consider that patients with SCD may also suffer health disparities due to socioeconomic factors, bias, discrimination, and a lack of doctor–patient communication (Meints et al., 2019). Patients of color may be disproportionately labeled as "drug-seeking," and because they are disproportionately represented among SCD patients, they may be at special risk of undertreatment for pain (Elander et al., 2004). For example, one earlier study of opioid prescribing across all conditions found that white patients were

significantly more likely to receive opioid prescriptions in EDs than black patients (Pletcher et al., 2008). Another study found evidence of provider bias specifically in treating black patients with SCD who were classified as having an opioid addiction (Elander et al., 2004). In addition to disparities in prescribing, there may be limited access to pharmacies that stock opioids in communities where SCD patients reside (Morrison et al., 2000).

There is some evidence that suggests that a home-based acute pain management setting for SCD is conducive to greater nonopioid medication use (e.g., NSAIDs and antidepressants) (Smith and Scherer, 2010).

As noted in the NHLBI report, analgesics other than opioids may be used to treat acute VOC pain. In efforts to reduce the risk of opioid use disorder and over-prescribing to treat SCD, one study found accumulating evidence that the use of N-methyl-D-aspartate receptor antagonists such as ketamine and lidocaine may decrease opioid consumption during SCD acute pain episodes (Puri et al., 2019). Ketamine added to morphine has also been shown to achieve better pain control and decrease the number of repeated doses of opioids (Alshahrani et al., 2019). Moreover, the FDA approval of L-glutamine oral powder in July 2017 (the second FDA-approved treatment for SCD) is projected to alter patients' incidence and management of SCD pain episodes.[8] The extent to which these new agents will result in less opioid prescribing without worsening pain control is unknown (Puri et al., 2019). More research on alternatives to opioid analgesics may lead to reduced use.

Finally, the CPG does not address opioid prescribing for acute VOC pain in specific patient populations such as patients with comorbidities and mobility issues. As these patient factors may influence their response and access to opioids, further research on such factors is warranted. Specifically, it would be helpful to expand studies that attempt to characterize SCD pain genotypes and phenotypes—including ischemic nociceptive, neurological, inflammatory, biobehavioral, and psychosocial factors—as they relate to developing nonopioid pain strategies.

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7

The Path Forward

The clinician caring for a patient whose acute pain cannot be adequately relieved with nonopioid approaches has two intertwined goals: to relieve the patient's acute pain and to minimize the adverse consequences of opioids for the patient receiving an opioid prescription, for third parties, and for the community. The experience of acute pain is highly variable and depends on many factors, such as the severity of the causative factor, the person's perception of the pain, and the effectiveness of treatment, including opioids. Acute pain may resolve with no or minimal intervention, but it may also require pharmacologic interventions, nonpharmacologic interventions, or both.

Patients for whom opioids are prescribed may be at risk for adverse outcomes including opioid misuse, chronic opioid use, and opioid use disorder. In addition, unused opioids may be available for misuse by family members or for diversion to others, further fueling opioid-related morbidity and mortality. Although opioids are effective for the management of acute pain, the continuing morbidity and mortality related to opioid analgesics in the United States underscores the need for evidence-based clinical practice guidelines (CPGs) to prescribe these medications safely, appropriately, and effectively.

The U.S. Department of Health and Human Services' Pain Management Best Practices Inter-Agency Task Force has emphasized the need for evidence-based acute pain management guidelines with this recommendation: "Encourage public and private stakeholders to develop acute pain management guidelines for common surgical procedures and trauma management, carefully considering how these guidelines can serve both to improve clinical outcomes and to avoid unintended negative consequences" (HHS, 2019, p. 22). The 2017 report by the National Academies of Sciences, Engineering, and Medicine (the National Academies), *Pain Management and the Opioid Epidemic*, began by explicitly calling attention to the two simultaneous public health challenges of "reducing the burden of suffering from pain and containing the rising toll of the harms that can result from the use of opioid medications" (NASEM, 2017, p. 1).

In response to the opioid epidemic in the United States, the U.S. Food and Drug Administration (FDA) tasked the National Academies committee with the following:

- Develop a framework to evaluate existing CPGs on opioid prescribing for acute pain;
- Identify existing opioid prescribing guidelines;
- Identify a prioritized list of specific surgical procedures and medical conditions associated with acute pain for which opioids are commonly prescribed;
- Evaluate selected existing opioid prescribing guidelines for acute pain using the framework to indicate whether they are sufficiently evidence-based; and
- Develop a prioritized research agenda that indicates deficiencies in the evidence base for the guidelines and what additional information would be required to have the guidelines meet the standards in the committee's framework.

ADDRESSING THE COMMITTEE'S TASKS

To accomplish the first task, the committee developed the frameworks presented in Chapter 4. Two frameworks were developed—an analytic framework that identifies the elements to determine which outcomes may occur following different opioid prescribing strategies and an evidence evaluation framework that provides an approach to determine how reliable and useful a study may be in assessing each element of the analytic framework. Chapter 4 also discussed the implementation, dissemination, and uptake of CPGs by health care providers and organizations. The committee considered the frameworks and approaches used by other organizations, particularly those of the U.S. Preventive Services Task Force (USPSTF) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, when developing its own frameworks. Several CPGs addressing opioid prescribing for acute pain were identified (e.g., AAPD, 2018; Qaseem et al., 2017; VA/DoD, 2017), but few of them provided specific evidence-based recommendations on the appropriate opioid dosage, the number of pills prescribed, and the duration of opioid use for a particular surgical or medical indication.

In response to its other tasks, the committee, with input from experts and stakeholders at its three public sessions, developed a list of surgical procedures and medical conditions that should be priority indications for the development of CPGs based on their public health impact. The public health impact of a particular indication was a function of its prevalence and how likely opioid over-prescribing was for that intervention, as over-prescribing results in pills that remain unused and available for diversion to unintended users. The prioritized surgical and medical indications were listed in Tables 5-2 and 5-3, respectively, along with a list of available guidelines for each indication.

In Chapter 6, the committee further evaluated the most relevant guidelines for three particular surgical indications and four medical indications. The guidelines were assessed against the analytic framework presented in Chapter 4. This analysis led to the identification of data gaps and research needs for each indication, which together formed the basis for the research agenda discussed in this chapter. In this chapter, the committee presents cross-cutting findings, conclusions, and recommendations based on the evidence presented in Chapters 4, 5, and 6.

A FRAMEWORK FOR EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES

Recommendation A: Professional societies; health care organizations; local, regional, and national stakeholders; and other developers of evidence-based clinical practice guidelines (CPGs) for opioid prescribing for acute pain should use an analytic framework (e.g., Figure 4-2) to identify and assess the evidence base for each CPG. The opioid prescribing strategies, intermediate outcomes, and health outcomes evaluated to develop the CPG should be explicitly described. CPGs should use a well-accepted methodology (e.g., the Grading of Recommendations

Assessment, Development and Evaluation [GRADE] approach) for grading the evidence and rating the strength of the recommendations.

As discussed in Chapter 3, there are several types of guidelines for opioid prescribing for acute pain. Chapter 5 provided examples of the guidelines that are publicly available for the indications the committee prioritized for guideline development. As was evident in Tables 5-2 and 5-3, not all of the listed guidelines meet the committee's definition of evidence-based CPGs.[1] Some guidelines are specific to acute pain, whereas others are focused on chronic pain with some recommendations on acute pain. Many are evidence-based, but others are based on expert opinions with or without supporting evidence, and some guidelines are developed on the basis of studies conducted by researchers at a single or several health care organizations. Some guidelines do not describe specific prescribing strategies that could be easily replicated by other clinicians (e.g., specifying only a maximum or initial quantity of opioid to be prescribed) or tailored to condition- or patient-specific characteristics. The guidelines may be based on data collected from organizational records (e.g., electronic health records [EHRs] and health insurance claims) and patient-reported outcomes, or they may be developed on the basis of in-depth, formal, systematic assessments of a body of published literature.

Although the committee's Statement of Task (see Chapter 1) asked it to address evidence-based CPGs developed and disseminated by medical specialty societies, the committee broadened its considerations of possible guideline developers to include other organizations that have developed opioid prescribing guidelines, policies, or regulations, such as health care organizations; federal, state, and local governments; state medical boards; health insurers; and even individual researchers. The committee recognized that the majority of evidence-based CPGs have been or will be developed by professional societies (medical and other health care professionals) for use by their members. Some guidelines, such as the Centers for Disease Control and Prevention (CDC) CPG for chronic pain, and those developed by professional societies are intended to be national in scope, whereas others apply primarily to a single health care organization (e.g., the Mayo Clinic). Some guidelines are specific regarding opioid prescribing (e.g., those of Colorado, the Michigan Opioid Prescribing Engagement Network [OPEN], Philadelphia, Oregon, and the Washington Bree Collaborative), whereas others are framed in broader terms of pain management or pharmacotherapies rather than opioid prescribing per se (e.g., those of the American Academy of Pediatric Dentistry [AAPD], the American College of Surgeons, and the American Geriatrics Society).

In addition to guidelines developed by professional societies or health care organizations, there are laws, regulations, and policies of various states, health insurers, and health care organizations, including state medical boards, that govern the actions of clinicians prescribing opioids for acute pain. As noted in Chapter 3, as of 2018, 33 states (NCSL, 2019) and several health insurers (e.g., Darshak Sanghavi, United Health, presentation to the committee, July 9, 2019) have restrictions on the amount of opioids that may be prescribed to a given patient or on the number of days that an opioid may be prescribed or on both; the federal Centers for Medicare & Medicaid Services also has policy guidelines on opioid prescribing (CMS, 2019). In spite of the number of states with prescribing limits on opioids, particularly those with restrictions on the length of prescribing for acute pain indications, there has not yet been a thorough study of the potential unintended and intended consequences that such prescribing limits may have with regard to decreasing the effectiveness of pain control and reducing opioid misuse,

[1] The committee adopted the definition of an evidence-based CPG as given in the 2011 Institute of Medicine (IOM) report *Clinical Practice Guidelines We Can Trust*, that is, "statements that included recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms or alternative care options" (IOM, 2011, p. 4).

overdoses, and death. The committee notes that recommendations on length of prescribing may be of limited usefulness in guiding clinician prescribing behavior because for many indications there is a lack of clarity regarding the quantity of opioids that constitutes a day's supply. This lack of clarity argues for the use of a common metric for opioid prescribing such as morphine milligram equivalents (MMEs) (see Recommendation G).

Several health care organizations, including Brigham and Women's Hospital, the Dartmouth-Hitchcock Medical Center, John Hopkins, and the Mayo Clinic, have also implemented opioid prescribing recommendations (Delgado et al., 2018; Holland et al., 2019; Thiels et al., 2017). These recommendations include specific guidance on opioid prescribing quantities for conditions and procedures, changes to the default number of pills prescribed in EHRs, and increased clinician and patient education. EHRs frequently have default settings for prescriptions, and modifications to EHR prescribing defaults may present an opportunity to reduce opioid prescribing for postsurgical discharge, while still giving surgeons the option to increase the quantity of opioid pills by providing a brief explanation (Stulberg et al., 2019).

Although many of these opioid initiatives have been implemented at a single health care organization or system (e.g., the Mayo Clinic), others have engaged multiple health care organizations, such as state health agencies, private industry, and insurers, to develop guidelines that span systems. For example, the Michigan OPEN in the state of Michigan and the Bree Collaborative in Washington State both have developed CPGs as collaborative efforts among researchers, clinicians, administrators, and regulators.

Regardless of who has developed guidelines on prescribing opioids for acute pain, the committee identified data gaps in each of the guidelines that argues for a more consistent approach to their development. The guidelines listed in Tables 5-2 and 5-3 varied from thoroughly researched guidelines that met many, but not all, of the standards laid out in the 2011 Institute of Medicine (IOM) report *Clinical Practice Guidelines We Can Trust*, to simply lists of opioid prescribing ranges for a particular indication. The committee notes that several of the guidelines followed a standardized development process that met some of the IOM standards for trustworthy CPGs, such as identifying any conflicts of interest for the developers, presenting the development methodology, and describing in detail the evidence on which the guideline was based. For example, CDC; the American Pain Society; the National Health, Lung, and Blood Institute; the American College of Occupational and Environmental Medicine; and the American Academy of Orthopaedic Surgeons have all developed evidence-based CPGs that discuss pain management, although not all of them specifically address opioid prescribing for acute pain.

The guidelines considered by the committee also varied in whether and how they addressed each of the key elements in the committee's analytic framework—that is, identifying the specific patient populations to which the guideline is applicable, presenting an evidence-based opioid prescribing strategy, identifying potential intermediate outcomes, and specifying the expected health outcomes associated with the strategy. With regard to patient populations, for many surgical and medical indications there is a lack of evidence on the outcomes of opioid prescribing strategies in such populations as the elderly, children and adolescents, minority populations, patients with chronic opioid use or opioid use disorder, and patients for whom first-line nonopioid medications are contraindicated (e.g., the use of nonsteroidal anti-inflammatory drugs [NSAIDs] in renal failure or following gastric bypass procedures). Although some guidelines have been developed for specific populations (e.g., pregnant women with opioid use disorder [ACOG, 2017] and the perioperative management of the geriatric surgical patient [Mohanty et al., 2016]), other guidelines may not specify when or how opioids should be used in such populations or how to manage acute pain. Even when there is evidence of different opioid prescribing needs for certain populations, the guideline may not address these differences in its recommendations. In many instances, opioid prescribing for acute pain may be stated simply as the lowest possible effective dose for the shortest time necessary, which does not provide either clinicians or patients with specific guidance.

Recommendations on the amount of opioids needed for particular acute pain situations, such as breakthrough pain or for patients who cannot use nonopioid alternatives, are not given.

Other important gaps in most guidelines include a lack of data on the amount of MMEs prescribed for patients relative to the amount used, patient reports of pain control and functioning, longer-term health outcomes such as possible transition from acute pain to chronic pain, chronic opioid use, and the development of opioid use disorder. Using a standardized CPG development process and presenting the information in a uniform format will facilitate the assessment of the impact of the CPG across multiple health outcomes (e.g., pain control, adverse effects, and public health harms) and indicate where further research is necessary.

Evaluating the evidence base for an opioid prescribing strategy is best accomplished using well-established approaches, such as GRADE. The committee recommends the GRADE approach because it is used widely, the study evaluation process is readily accessible online, and there are clear instructions for its use. Furthermore, GRADE provides an accepted, robust, and systematic approach to evaluating evidence with explicit criteria for evaluating studies that support a CPG. The GRADE method is used by numerous organizations, such as USPSTF, the World Health Organization, and the Agency for Healthcare Research and Quality.

DEVELOPING CLINICAL PRACTICE GUIDELINES FOR OPIOIDS

Appropriate Use of Opioids and Nonopioid Interventions

Recommendation B: Developers of evidence-based clinical practice guidelines (CPGs) for an acute pain indication should address the appropriate use of opioids for the indication as well as the optimal opioid prescribing strategies. CPGs should explicitly state the role of opioid alternatives, such as acetaminophen or nonsteroidal anti-inflammatory drugs, as first-line therapies and the role of opioids in the context of nonopioid pharmacologic and nonpharmacologic alternatives.

Researchers who evaluate opioid prescribing strategies for an acute pain indication should also specify any other interventions, including nonopioid interventions, used to relieve pain in the patient populations to be studied.

Because opioids may not always be appropriate for acute pain indications or patients, it is important that CPGs address when to use them in addition to identifying which specific opioids to use (e.g., hydrocodone versus oxycodone), and what dose and duration to use. For many surgical and medical indications, such as vaginal delivery and low back pain, evidence shows that opioids are no more effective for relieving acute pain than nonopioid interventions (see Chapter 6). As discussed in Chapter 4 and demonstrated in Chapter 6, many CPGs consider the use of opioids for pain control in the context of a broader nonopioid and nonpharmacologic approach to pain management. For example, the CPG for low back pain developed by the American Pain Society recommends the use of nonopioid interventions (Qaseem et al., 2017). The American College of Obstetrics and Gynecology recommends the use of cold packs for perineal analgesia, reserving opioids for breakthrough pain (ACOG, 2018).

However, evidence gaps remain regarding the role of opioids in the context of alternative strategies, particularly with respect to timing and dosing. Many studies that evaluate opioid prescribing do not mention other interventions that may be prescribed to or used by the patient, including the use of over-the-counter medications, the administration of local anesthetics, and interventions such as yoga and

acupuncture. For example, numerous studies describe the effect of enhanced-recovery-after-surgery pathways using nonopioid and nonpharmacologic interventions (including multimodal approaches such as regional anesthesia and injections) for pain management following procedural care. These studies highlight the role of opioid alternatives, such as NSAIDs, acetaminophen, and gabapentinoids, alongside opioid analgesics in the management of acute pain. A greater body of evidence regarding the comparative effectiveness of these strategies could inform the role of opioids for acute pain and provide guidance concerning their role in the context of alternative interventions.

The committee recognizes that obtaining and reporting such information may be difficult, particularly for interventions that may be prescribed by clinicians in other health care settings (e.g., determining if NSAIDs have been prescribed by a primary care provider for a surgical patient) or for interventions used by the patient but not noted in the EHR (e.g., acupuncture, meditation). The increased use of EHRs, however, may help reduce the burden of collecting such data, particularly for patients who receive their care at integrated health care systems. As there is always the potential for adverse or synergistic effects, reporting on all potential interventions can provide more accurate data on the long- and short-term outcomes of opioid prescribing.

Patient Population Considerations

Recommendation C: Developers of evidence-based clinical practice guidelines (CPGs) for outpatient opioid prescribing for acute pain indications should explicitly state the patient populations to which the CPG is applicable (e.g., adults versus children) and those subpopulations for whom the CPG recommendations may need to be modified such as, for example, patients with comorbidities, prior opioid exposure, or opioid use disorder. CPG developers should also explicitly define the contextual aspects of prescribing, such as setting, prescriber type, and prior treatments.

The analytic framework given in Chapter 4 requires that the patient populations and surgical and medical indications to be evaluated be explicitly stated. However, given the current knowledge gaps and the burden of morbidity and mortality because of opioid use, there may be little or no data on intermediate or health outcomes for some populations in the literature.

As discussed in Chapter 3, acute pain, its management, and its associated outcomes are patient and setting specific (Bjorland et al., 2017; Nobrega et al., 2018; Radcliff et al., 2017; Rahim-Williams et al., 2007; Smith et al., 2019), and the context in which a patient presents with pain is dependent on many factors that will affect both how patients perceive their pain and how they respond to treatment. Although a guideline for opioid prescribing for an acute pain indication might result in reduced opioid use while providing adequate relief of pain across an entire population, a particular patient or subpopulation of patients (e.g., obese patients) may not experience the same benefits and might require prescribing adjustments (Chua et al., 2019; Schug and Raymann, 2011). For acute pain, individualized pain management is complicated by the many factors that may influence opioid requirements, including patient demographics, the underlying cause of the pain, prior pain history, substance use history, opioid use history, comorbid psychiatric and medical conditions including kidney and liver impairment, the duration of the symptoms, clinical settings, the use of nonopioid therapies, and other factors. As noted in the discussion of Recommendation B, not all opioids may be suitable for all patients. Consideration should be given to patient characteristics and situations that may affect or support the use of certain opioids, such as substance use disorder or allergies or an inability to follow prescribing directions. For example, in women who have postpartum pain and wish to breastfeed their infants, the use of codeine

is not recommended as it causes excessive maternal sedation and may cause serious adverse effects in the nursing infant; tramadol is also not recommended because its pharmacologic properties are similar to codeine (AGOG, 2018).

As discussed in Chapters 4 and 5, the contextual aspects of the health care setting may also influence treatment decisions. For example, opioids may be prescribed for acute pain following surgical care performed as an inpatient or prescribed at discharge for outpatients following ambulatory surgery. Other acute pain indications, including many medical indications such as renal stones and fractures, may first present in emergency departments (EDs) or urgent care facilities or, for indications such as migraine headache and low back pain, in a primary care clinician's office. Prescribing can be influenced by the resulting differences, such as the episodic or longitudinal nature of patient–provider relationships, the duration of care (inpatient stay versus outpatient care), or the availability of subspecialist care.

To date, CPGs for many indications for opioid prescribing for acute pain lack granularity regarding these nuances in care. For example, CPGs for obstetrics could encompass prescribing across perinatal care, postoperative care, and outpatient follow-up visits. Other CPGs, such as the guideline for sickle cell disease, have recommendations on treatments for inpatients, EDs, and at home. For example, the CPG for pain management in patients with sickle cell disease provides no opioid prescribing recommendations for patients who are discharged from inpatient or ED care to home (NHLBI, 2014). Studies suggest that ED clinicians are among the top prescribers of opioids (Barnett et al., 2017; Volkow et al., 2011), and CPGs have been developed for them (ACEP, 2017). Other setting-specific guidelines are the American Dental Association recommendations on treating acute pain resulting from dental procedures, particularly third molar extractions (ADA, 2018), and the AAPD policy document that states that "combining opioid analgesics with NSAIDs or acetaminophen for moderate to severe pain may decrease overall opioid consumption" (AAPD, 2018, p. 102). CPGs need to be clear about the setting for which the opioid prescribing recommendations pertain and should distinguish between those for inpatient, ED, and discharge situations.

Evidence Linkages

Recommendation D: Researchers who conduct studies to determine optimal opioid prescribing strategies for acute pain should examine not only the intermediate outcomes (e.g., pills prescribed and unused and long-term opioid use), but also the short- and long-term health outcomes (e.g., mortality, overdose, opioid use disorder, pain, and function) at both the patient and population levels.

Developing CPGs for acute pain following surgical care is an important opportunity to reduce unnecessary prescriptions, prevent the prolonged use of opioids, and optimize postoperative pain management. Recently, studies have demonstrated wide variation in opioid prescribing within procedures and indications for surgery and some approaches for reducing postsurgical opioid use (Berger et al., 2019; Eid et al., 2018; Hill et al., 2017; Howard et al., 2018a; Thiels et al., 2017). Moreover, there is substantial evidence suggesting that for many surgical procedures, opioids are prescribed in excess (Hill et al., 2017; Howard et al., 2018a,b; Kim et al., 2016; Lee et al., 2019; Sabatino et al., 2018). However, it is often challenging to balance sufficient opioid prescribing to relieve acute pain with preventing the adverse effects associated with having unused pills (which can be diverted for unintended use) and with prolonged use, misuse, and abuse (Bicket et al., 2017). On the one hand, guidelines and policies that are more restrictive regarding the MMEs in an initial prescription for acute pain (such as those of many states) may lead to fewer unused pills available for misuse or diversion (Bicket et al., 2017, 2019;

Prabhu et al., 2018; Thiels et al., 2017). On the other hand, such guidelines also may result in more patients having severe acute pain that persists beyond the initial prescription and thus needing a refill or requiring a follow-up phone call, clinic visit, or ED visit (Chiu et al., 2018; Reid et al., 2019; Thiels et al., 2017). These differences have an impact on patients, communities, and society more broadly, and it is critical to consider each of these outcomes when developing CPGs. Attention to patient-centered outcomes, such as improved functional status or return to work, may be more important for some patients than complete pain relief, and may offer an opportunity to reduce individual and population-level risks of long-term or excessive opioid use.

CPG developers may also examine basic research on the tolerance, dependence, and addiction potential of opioids. This information should be considered when conducting the systematic review of the literature as described in Chapter 4. The committee recognizes that different opioids are metabolized differently; have different mechanisms of action for pain relief, tolerance, and addiction; and these mechanisms, and the populations likely to be at risk, need to be considered when recommending an opioid prescribing strategy in a CPG.

For guideline developers to strike an appropriate balance between relieving acute pain and reducing the number of unused opioids, evidence is needed on the relevant intermediate outcomes and their links to health outcomes at both the patient and community levels (Wolff et al., 2018). Currently, however, there is little evidence to link lower opioid MME prescriptions to population-level outcomes, such as opioid use disorder and opioid overdoses.

Guideline Implementation

Recommendation E: Organizations that develop evidence-based clinical practice guidelines (CPGs) on opioid prescribing for acute pain, including governmental entities (federal, state, and local) and nongovernmental entities, such as professional societies, health care organizations and collaboratives, and health insurers, should establish a process for disseminating, implementing, and monitoring the uptake and impacts of the CPG on opioid prescribing practices. These impacts include short- and long-term patient and population-level intermediate and health outcomes, particularly opioid misuse, opioid use disorder, and opioid overdoses and deaths.

The 2011 IOM report *Clinical Practice Guidelines We Can Trust* emphasized that simply developing an evidence-based CPG does not ensure that it will have the desired impact on patient health and well-being. To improve the uptake of CPGs by clinicians and health care organizations, guideline development groups should strive to develop recommendations that are clear and actionable. The committee found that although guidelines may be available for some indications, there is evidence to suggest that guidelines are not always followed (Khalid et al., 2015). Recommendations that are based on high-quality evidence have greater acceptance and uptake than those based on lower-quality evidence (Hoesing, 2016; Mazrou, 2013; Murad, 2017).

Promoting the uptake of CPGs into clinical practice may require the development of strategies to expand their use through clinician education, clinical decision support tools, and other resources. The reasons for any lack of adherence and uptake should be investigated. Guideline developers should also consider implementation strategies, such as the development of tools to facilitate use by clinicians (e.g., algorithms, calculators, pocket guides, and Web-based applications), efforts to support integration of CPGs into clinical workflow through EHR dashboards or other tools, and dissemination activities such as webinars, journal publications, meeting presentations, and resources to support continuous quality improvement (QI) activities.

An evidence-based CPG that presents opioid prescribing strategies that are acceptable to both clinicians and patients also will reach a broader audience. Educating patients about pain management is an integral aspect of aligning patients' expectation about pain control with opioid prescribing practices. As noted in Chapter 4, a multidisciplinary patient education effort that engages clinicians and other health care providers including nurses and pharmacists may be effective in reducing opioid prescribing without sacrificing patient satisfaction with their pain control (Kaafarani et al., 2019). These health care providers can educate patients and their caregivers about the benefits and harms of opioids, ensure patients understand how to take them appropriately, and explain that the elimination of all pain may not be a feasible or necessary goal when taking opioids. Such education may be particularly valuable for populations that are already vulnerable to opioid harms, such as patients with chronic pain who already use opioids, patients with substance use disorders, or those with mental health issues.

In light of the ongoing opioid overdose epidemic, there is a need to not only provide patients with the best possible pain control, but also to improve public health by reducing the opportunities for opioid diversion, misuse, overdose, and death. This can be accomplished by monitoring relevant outcomes at the patient and population levels. The committee reviewed many studies that reported on the short- and long-term intermediate effects of reduced opioid prescribing in various health care systems (e.g., Hill et al., 2017; Thiels et al., 2017); several of these studies also report health outcomes in terms of patient reports of satisfaction with their care and pain control. However, there is a paucity of studies that examine the effects of opioid prescribing strategies on population-level outcomes, such as fewer opioid overdoses seen in the ED, fewer first responders using naloxone rescue therapy, and fewer opioid-related deaths in the community. Although efforts to address the opioid overdose epidemic underpin many of the strategies to reduce opioid prescribing, the societal impacts of such strategies are not clearly understood and require further research. The committee appreciates that such studies may be challenging to conduct, particularly efforts to link the introduction of CPGs to distal population-level health outcomes, such as opioid use disorder and opioid overdose deaths. While it seems intuitive that reducing opioid prescribing may result in fewer opioid overdoses and deaths, the impact of such reductions on patient pain control and the risk of unintended consequences for patients, their support systems, and their communities cannot be assumed and should be informed by accurate and comprehensive data. Such unintended consequences may include the increased use of illicit and more potent opioids should fewer prescription opioids be available, which in turn may lead to more opioid overdoses and death (NASEM, 2017).

Furthermore, as the awareness of opioid-related morbidity and mortality has increased, CPGs will need to address the new literature. Thus, it is important for guideline developers to include a plan for monitoring the literature for new evidence and updating the guidelines on a periodic or as-needed basis when new information suggests that changes in prescribing practices are warranted. This underscores the need to have a dynamic framework that can adjust as the knowledge of pain management and opioid stewardship grows in the coming years. As additional research is carried out, organizations that produce CPGs on opioid prescribing for acute pain can modify their guidelines to take into account new evidence and strengthen the effectiveness of the CPG.

Increased efforts to link government and private data resources can also provide new information on prescribing practices, patient outcomes, and community outcomes. Private–public partnerships between all levels of government (including health departments, medical societies or boards, and law enforcement) and academic and health care system researchers can help identify short- and long-term adverse effects, morbidity, and mortality resulting from current and future opioid use. Examples of such partnerships include a Massachusetts effort to simultaneously analyze 10 state datasets with information on opioid deaths in the state (Bharel, 2016) and join research efforts between FDA and academic researchers to review health care records in the database of a large national health insurer (i.e., Optum's

Clinformatics DataMart™ [Mundkur et al., 2018]). To ensure that the CPG reaches a broad audience, the committee encourages guideline developers to consider collaborative, multidisciplinary CPG efforts such as *Optimal Perioperative Management of the Geriatric Patient: Best Practices Guideline from ACS NSQIP/American Geriatrics Society* (Mohanty et al., 2016).

To avoid unintended consequences resulting from the inappropriate use of a CPG, guideline developers should clearly describe the patients and settings for which recommendations apply. Furthermore, they should work with policy makers to ensure appropriate implementation, and monitor the impacts of CPGs on clinical practice and health outcomes to ensure that they are applied in the manner for which they were intended.

DEVELOPING THE EVIDENCE BASE

Study Design

Recommendation F: Researchers studying opioid prescribing for acute pain should address evidence gaps by linking opioid prescribing strategies to health outcomes using appropriate study designs. Well-designed observational and quality improvement initiatives are helpful for evaluating the effects of opioid prescribing strategies on health outcomes.

Evidence-based CPGs require the identification, review, synthesis, and ranking or grading of the evidence to support the opioid prescribing recommendations for an indication. As discussed in Chapter 4, multiple types of evidence can be used to support guidelines, such as randomized controlled trials (RCTs), observational studies, and QI initiatives. Although RCTs, which produce the most rigorous type of evidence, have been conducted for a few indications, the urgency for generating information on best practices to help curtail the opioid epidemic demands efficient models to generate the necessary evidence to improve care expeditiously. Moreover, the committee notes that conducting RCTs for many prescribing strategies may be precluded, given the logistical, ethical, and financial constraints of those trials. There is an increasing number of observational studies and assessments of QI initiatives regarding opioid prescribing that may provide evidence for CPGs. The strengths and limitations of each of these evidence sources are discussed briefly below.

Randomized Controlled Trials

Evidence from RCTs for opioid prescriptions for acute pain has several methodological strengths and weaknesses. The major strength of RCTs is that they provide the most robust evidence of cause and effect—that is, that different prescribing strategies may produce different outcomes. Evidence for causality is strong because the randomization of patients to the study arms controls for baseline differences between the two strategies. Thus, ideally the only difference between the two arms is the assignment to the intervention or control group.

However, RCTs also have certain limitations that may restrict their use. They are typically resource intensive, require the recruitment of an appropriate patient population that must meet enrollment criteria, are lengthy to conduct, and their results may not be applicable to the general patient population. Furthermore, RCTs may be difficult to conduct for relatively uncommon indications, such as sickle cell disease, because the affected population may be a minority group, there may be few patients at any given health care research facility, or the patients may not trust the health care establishment (Smith, presentation to

committee, July 9, 2019). RCTs also may not be able to assess relatively rare, but clinically important health outcomes such as opioid misuse, opioid use disorder, and overdose.

Observational Studies

Observational studies can be retrospective or prospective and can assess the effects of opioid prescribing over time or across populations. Observational studies can be designed to evaluate QI initiatives such as patient and provider education, changing the EHR defaults or organizational policies for opioid prescriptions, and increasing the use of nonopioid medications and nonpharmacologic approaches. Studies employing observational designs should include appropriate comparator groups and strategies to specify and account for confounding factors.

Compared with RCTs, the strengths of observational studies are that they are usually less resource intensive, they include populations that are more representative of the range of patients seen in clinical practice (e.g., a diverse population with regard to age, sex, comorbidities, use of concomitant treatments, and race or ethnicity) (Corrigan-Curay et al., 2018), they use larger study populations and therefore may have greater statistical power to detect infrequent outcomes (such as chronic opioid use after acute pain in opioid-naïve patients), and they can be used to study special populations (e.g., people using chronic opioids or with opioid use disorder, pregnant women, children and adolescents, those from socially disadvantaged communities, or from geographical areas that have high rates of opioid use disorder and opioid overdoses).

As with RCTs, observational studies have limitations. These can include poor validity, measurement bias, observation bias, recall bias, population attrition, low levels of follow-up, reliance on patient-reported outcomes for past events such as pain intensity, confounding factors (e.g., pre-existing opioid use), and poor response rates. In addition, interventions and outcomes may lack clarity, particularly for data gathered for purposes outside of research. For example, although many study types rely on administrative data, these often lack the granularity and accuracy needed to develop prescribing guidelines due to challenges with accurate coding. In addition, administrative data may not capture patient-reported outcomes such as pain control, function, and quality of life.

Quality Improvement Initiatives

In addition to evidence-based CPGs for prescribing opioids, health care organizations and consortia have used QI initiatives to provide evidence for some of the key linkages in the analytic framework. QI initiatives typically complete data collection and analysis in a shorter time than can an RCT (Pletcher et al., 2014). Moreover, the QI results may be more directly and promptly applied to improve clinical practice. For example, the Michigan Surgical Quality Collaborative and Michigan OPEN used QI measures to develop and disseminate prescribing guidelines for nine surgical procedures (PDOAC, 2018). Follow-up of prescribing practices after release of the guidelines showed that the amount of opioids prescribed and the opioid consumption were both reduced and that neither patient satisfaction with the surgery nor pain ratings in the first week after surgery were significantly changed (Vu et al., 2019).

Reporting Opioid Prescribing Strategies

Recommendation G: Researchers should specify opioid prescribing strategies in a standardized manner, including the drug, strength, amount, and duration of the opioids. Reporting opioid prescriptions as morphine milligram equivalents (MMEs) would facilitate evaluation of different opioids based on analgesic potency.

As noted in the discussion of Recommendation A, there is a lack of consistency in reporting opioid doses or durations that may make it difficult to compare findings among studies. Sometimes only the number of pills prescribed or the duration of therapy is provided, without information on the drug and strength prescribed. For this reason, MMEs are recommended as a means to standardize reporting, and details on how MMEs were calculated should be provided (Rennick et al., 2016). As reported in Chapter 1, 50 MMEs per day is equal to 50 mg of hydrocodone (10 tablets of hydrocodone/acetaminophen 5/300) or 33 mg of oxycodone (~2 tablets of oxycodone sustained-release 15 mg). Furthermore, patients may receive different types of opioids that come in different strengths. For example, Barteis et al. (2016) found that following cesarean delivery, patients were prescribed hydrocodone, hydromorphone, or oxycodone at discharge that ranged from 254 to 284 MMEs, and following thoracic surgery, the MMEs prescribed at discharge ranged from 564 to 986, and four different opioids were prescribed. The committee suggests that converting the opioid prescription to MMEs in research studies would facilitate evidence evaluation and study comparisons.

PRIORITIZING INDICATIONS

Recommendations H: Professional societies, health insurers, and health care organizations should consider the prioritized surgical and medical indications listed in Table 7-1 for evidence-based clinical practice guidelines (CPGs) development or, where a CPG already exists, for modification to meet the analytic and evidence frameworks in this report. The committee acknowledges that other surgical and medical indications may emerge as priorities as the evidence base grows.

FDA requested that the committee identify and prioritize surgical and medical indications that are associated with acute pain and for which opioid analgesics are commonly prescribed and considered clinically necessary. In addition, the committee was asked to recommend where evidence-based CPGs would help inform prescribing practices. The committee found that there are numerous relatively prevalent surgical procedures and medical conditions for which opioids are commonly prescribed for acute pain. In response to its tasks, the committee began by identifying surgical procedures for which opioids are commonly prescribed at discharge. Opioid administration in the immediate postsurgical period while the patient is in recovery or is an inpatient was not considered for this report because it is outside the committee's Statement of Task and there is less opportunity for misuse or diversion. Medical indications for which opioids are commonly prescribed for acute pain were more difficult to identify, but some studies indicated that opioids are commonly prescribed in EDs and primary care settings for indications such as low back pain, headache, and renal stones. Studies conducted by several health care organizations have shown that opioid prescribing for both surgical and medical indications frequently results in unused pills (see Tables 5-2 and 5-3). The tables also highlight the variability in guidelines that are available for these indications, ranging from evidence-based CPGs to a single study published in a medical journal. The priority surgical and medical indications for CPG development are given in Table 7-1.

Although the committee used the prevalence of an indication and evidence of opioid over- or under-prescribing as the criteria for prioritization, it recognizes that some organizations may have other criteria for prioritizing topics for CPG development. Such criteria may include indications frequently associated with opioid misuse, new treatments to replace opioids, or patient and provider preference.

The committee recognizes that the management of acute pain from different surgical procedures or indications might be addressed in a single aggregated CPG (see Chapter 5). For example, it may be possible that the acute pain following one laparoscopic procedure is similar in intensity and duration to

TABLE 7-1 Priority Indications for Acute Pain for Clinical Practice Guideline Development or Modification (listed alphabetically)

Surgical Indications	Medical Indications
Anorectal, pelvic floor, and urogynecologic (e.g., colon resection, hemorrhoidectomy, vaginal hysterectomy)	Dental pain (nonsurgical)
Breast procedures (e.g., lumpectomy, mastectomy, reconstruction, reduction)	Fractures
Dental surgeries (e.g., third molar extraction)	Low back pain (includes lumbago, dorsalgia, backache)
Extremity trauma requiring surgery (e.g., amputation, open reduction and internal fixation)	Migraine headache
Joint replacement (e.g., total hip arthroplasty, total knee arthroplasty)	Renal stones (also called kidney stones, nephrolithiasis, calculus of the kidney, renal colic)
Laparoscopic abdominal procedures (e.g., appendectomy, bariatric surgery, cholecystectomy, colectomy, hysterectomy, prostatectomy)	Sickle cell disease
Laparoscopic or open abdominal wall procedures (e.g., femoral hernia, incisional hernia, inguinal hernia)	Sprains/strains, musculoskeletal
Obstetric surgeries (e.g., cesarean delivery, vaginal delivery)	Tendonitis/bursitis
Open abdominal procedures (e.g., appendectomy, cholecystectomy, colectomy, hysterectomy)	
Oropharyngeal procedures (e.g., tonsillectomy)	
Spine procedures (e.g., fusion in both adults and children, laminectomy)	
Sports-related procedures (e.g., anterior cruciate ligament repair and reconstruction, joint arthroscopy, rotator cuff repair)	
Thoracic procedures (e.g., thoracoscopy, repair of pectus excavatum in children [Nuss procedure])	

that following a different laparoscopic procedure and therefore that opioid prescribing strategies might be similar for both procedures. The CPG development process is not prescriptive in its approach as to which indications might be appropriate to aggregate (see Chapter 5 for more information on aggregating indications) or what extrapolations from one indication or population to another are most appropriate. However, decisions to aggregate or extrapolate indications in guidelines should be based on an explicit rationale from guideline developers, such as the nature of the procedure, the duration of surgery, the extent of tissue damage, or opioid prescribing practices being similar across the aggregated indications. Furthermore, there should be evidence that a single opioid prescribing strategy has similar intermediate and patient health outcomes for each procedure that is covered in the aggregate guideline. For example, one guideline might seek to aggregate laparoscopic surgery for appendicitis and cholecystitis. The aggregation and extrapolation of studies might bolster the applicability and implementation of CPGs for opioid prescribing for acute pain by expanding the available evidence on which they are based. Without such aggregation and extrapolation, it is less likely that a cogent approach would be developed for the many varied surgical and medical indications requiring opioid therapy.

A RESEARCH AGENDA FOR OPIOID PRESCRIBING FOR ACUTE PAIN

Recommendation I: Researchers studying opioid prescribing for acute pain should assess how nonopioid interventions (pharmacologic or nonpharmacologic, or both) affect the need for opioids as well as their effects on intermediate outcomes and health outcomes.

Many health care organizations are reducing their use of opioids and turning to other interventions to control pain. There are many interventions that are being explored for acute pain control, both pharmacologic and nonpharmacologic. For example, new interventions for postsurgical pain control that reduce reliance on opioids include peripheral nerve blockades for total knee arthroplasty (AAOS, 2015), the use of gabapentinoids for postoperative pain management (Hah et al., 2018), and enhanced recovery after cesarean delivery (Peahl et al., 2019). Research on such interventions may be particularly helpful for at-risk populations, such as obese patients in whom the use of postsurgical opioids must be closely monitored (Lloret-Linares et al., 2013; Schug and Raymann, 2011). New guidelines on third molar extractions recommend the use of NSAIDs as a first-line treatment (AAOMS, 2007), as is also the case for renal stones (Türk et al., 2016). Many nonpharmacologic interventions (e.g., acupuncture, heat/cold packs, physical therapy, and transcutaneous electrical nerve stimulation) may also be used as either adjuvants or alternatives to opioids. The committee recognizes that there are numerous nonopioid and nonpharmacologic interventions for pain control and that it may be difficult to conduct well-designed observational studies, let alone RCTs, to compare these interventions with opioids. Nevertheless, such studies may be useful for assessing interventions that are widely used in clinical practice. Comparative effectiveness research studies may also be useful. Such studies would help determine not only if opioids should be the first-line treatment for some indications, and if so, which ones provide optimal outcomes, but also which, if any, nonopioid alternative treatments might reduce opioid use and adverse outcomes. Compounding the issue of using nonopioids to treat acute pain is the fact that many health insurers either do not cover nonpharmacologic interventions or else cover them only to a limited extent and that the copay for some covered services may be prohibitively high for some patients.

Recommendation J: Researchers studying opioid prescribing for acute pain should address the evidence gaps in the following key priority areas:

- **outcomes of opioid prescribing strategies in key patient populations;**
- **the impact of clinical setting on opioid prescribing strategies; and**
- **the links between intermediate outcomes, such as the number of unused pills or long-term opioid use, and health outcomes, such as pain, mortality, overdose, opioid use disorder, and function.**

Few of the opioid prescribing guidelines reviewed in this report discuss the different prescribing needs of subpopulations, and this lack of guidance can result in inappropriate prescribing for some patients. As more research is conducted on how people metabolize and react to opioids and the potential genetic differences in opioid metabolism and physiology (see Chapter 2), there is a greater need to address these variations in evidence-based CPGs. Research shows that the elderly have different opioid needs than younger adults (Santosa et al., 2019). Comorbidities can also affect the use of opioids or other nonopioid interventions. For example, research might examine whether people with kidney disease have more risks of adverse effects when using NSAIDs than when using opioids for acute pain. More research on how different populations react to acute pain and to opioid treatment, including the influence of pain biomarkers and genomic variations, will help in personalizing treatment and reducing

opioid over-prescribing. Basic research on how opioids cross the blood–brain barrier, and on the differences in the pharmacodynamics of the various types of opioids will all help refine and optimize opioid prescribing for acute pain.

Similar research is needed to identify factors that can help align opioid prescribing practices in various settings with CPG recommendations. Such research might include determining if clinician and patient education or the use of reduced prescribing defaults in the EHR are effective approaches to reducing inappropriate opioid prescribing.

Research on whether the reduced opioid prescriptions recommended in CPGs will provide adequate pain relief to patients is also needed. Chapter 2 showed that while a majority of patients with an acute pain indication do not require more than a certain number of MMEs, some percentage of patients—around 20%, depending on the indication and the opioid prescribing amount in the guideline—do not have adequate pain control and need further assessment or an opioid refill. In order to adequately achieve the dual aims of relieving acute pain and reducing the harms of opioids, researchers need to examine whether patients who continue to have pain are able to access additional care to adequately relieve their pain. This issue may become more pressing as new opioids are approved and enter the market, as was recently the case for Dsuvia, a sublingual formulation of sufentanil (Gottlieb, 2018). New research will be required to determine the appropriate use of these new and potentially more potent and addictive opioids. Basic research on the mechanisms of action of these opioids on brain chemistry and their potential for tolerance, dependence, and addiction will need to be conducted. Evidence will also be needed to determine if these new opioids can be used as replacements for or supplements to existing opioid and nonopioid treatments. In light of the widespread disparities in access to health care in the United States, it is important that vulnerable populations have access to additional evaluation if their acute pain does not resolve satisfactorily.

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Appendix A

Committee Biographical Sketches

Bernard Lo, M.D. (*Chair*), is the president of The Greenwall Foundation, whose mission is supporting bioethics research and young researchers in bioethics. He is also a professor emeritus of medicine and the director emeritus of the Program in Medical Ethics at the University of California, San Francisco (UCSF). A member of the National Academy of Medicine, Dr. Lo served on the Institute of Medicine (IOM) Council and chaired the National Academies of Sciences, Engineering, and Medicine's Board on Health Sciences Policy. He chaired the IOM committees Sharing Clinical Trial Data (2015) and Conflicts of Interest in Medical Research, Education, and Practice (2009). He co-chairs the Standards Working Group of the California Institute for Regenerative Medicine, which recommends ethics standards for publicly funded stem cell research in California. Dr. Lo serves on the board of directors of the Association for the Accreditation of Human Research Protection Programs and on the medical advisory panel of Blue Cross/Blue Shield. Formerly he was a member of the National Bioethics Advisory Commission, the National Institutes of Health Recombinant DNA Advisory Committee, and the ethics subcommittee of the Centers for Disease Control and Prevention. Dr. Lo and his colleagues have published around 200 peer-reviewed articles on ethical issues concerning decision making near the end of life, oversight of research, the doctor–patient relationship, and conflicts of interest. He is the author of *Resolving Ethical Dilemmas: A Guide for Clinicians* (6th ed., 2019). He continues to care for a panel of primary care internal medicine patients at UCSF. Dr. Lo received his M.D. from Stanford University.

Mark C. Bicket, M.D., is an assistant professor of anesthesiology and critical care medicine at the Johns Hopkins University School of Medicine and is the director of the Multidisciplinary Pain Medicine Fellowship Program and the director of the Divisional Safety and Quality Assurance Program at Johns Hopkins. He also is a core faculty member of the Johns Hopkins Bloomberg Center for Drug Safety and Effectiveness. Dr. Bicket focuses his clinical expertise and research on interventional pain management with the goal of improving treatment options for patients with chronic and persisting pain. His research and work have been published in the *Journal of the American Medical Association* (*JAMA*), *British Medical Journal*, *JAMA Surgery*, *Anesthesiology*, *Regional Anesthesiology and Pain Medicine*, and *The Spine Journal*, among others. He recently published a review in *JAMA* that discussed the need for more

personalized pain management to avoid over-prescribing opioids and reduce risks linked to improperly stored opioids in the home. He also attends in operating rooms, with an emphasis on care under the enhanced recovery after surgery and obstetrical anesthesiology services. He is a member of the American Society of Anesthesiologists, the American Pain Society, and the American Academy of Pain Medicine. Dr. Bicket obtained his M.D. from the Johns Hopkins University School of Medicine, performed a pain management fellowship at Massachusetts General Hospital, and maintains board certifications in both pain medicine and anesthesiology from the American Board of Anesthesiology.

Nicholas W. Carris, Pharm.D., BCPS, is an assistant professor in the University of South Florida (USF) Health Taneja College of Pharmacy and the USF Health Morsani College of Medicine. As a board certified pharmacotherapy specialist, Dr. Carris has significant training and expertise in drug therapy. He has completed literature evaluations and has published an evaluation of implementing a new guideline recommendation. Dr. Carris has collaborated with a regional accountable care organization to implement the Centers for Disease Control and Prevention's opioid use guidelines. As part of this effort, he worked with key stakeholders and physicians to emphasize deprescribing. Dr. Carris is a member of the American College of Cardiology, the American Heart Association, the Florida Society of Health-System Pharmacists, and the American College of Clinical Pharmacy (ACCP), and the ACCP Ambulatory Care Practice and Research Network (Ambulatory Care PRN). Dr. Carris serves on a subcommittee in the Ambulatory Care PRN that awards seed grants as well as scholarships to members to attend training programs regarding grant writing or general research. Dr. Carris received his doctor of pharmacy degree from the University of Florida College of Pharmacy.

Roger Chou, M.D., is the director of the Pacific Northwest Evidence-Based Practice Center, a professor of medical informatics and clinical epidemiology and medicine, and a practicing internist at Oregon Health & Science University (OHSU). His primary clinical research areas are screening and prevention, the evaluation and management of pain, HIV/hepatitis C, and diagnostic testing. Dr. Chou has conducted more than 60 systematic reviews used by various organizations to formulate research agendas, develop clinical practice guidelines, and inform health care policy and clinical practice. He led a review commissioned by the Agency for Healthcare Research and Quality (AHRQ) on prescribing opioids for chronic pain; the Centers for Disease Control and Prevention (CDC) commissioned an update of this review to develop its recently issued guidelines on prescribing opioids for chronic pain. Dr. Chou served as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologist for 2016 CDC opioid guidelines and was a member of the steering committee. In addition to leading numerous evidence-based practice center (EPC) reviews for the AHRQ Effective Health Care Program, Dr. Chou has led OHSU's work supporting the U.S. Preventive Services Task Force (USPSTF) since 2010 and, just this year, was awarded a 3-year contract to conduct seven prevention and counseling systematic reviews for USPSTF in collaboration with other EPC faculty and staff. Dr. Chou also conducts research on systematic review methods and best practices, and he serves as the GRADE methodologist for the World Health Organization's (WHO's) Division of Reproductive Health, is the GRADE methodologist and a member of the WHO guideline development group for the diagnosis and treatment of viral hepatitis, and is a longstanding member of the Cochrane Back Review Editorial Board (currently serving as coordinating editor). Previously, Dr. Chou served as the director of the American Pain Society's Clinical Practice Guidelines Development Program and as a member of the American College of Physicians Clinical Practice Guidelines Committee. Dr. Chou received his medical degree from the Northwestern University Medical School, and he completed an internal medicine residency at OHSU and a health services research fellowship at the U.S. Department of Veterans Affairs Portland Health Care System.

M. Kit Delgado, M.D., M.S., is an assistant professor of emergency medicine and epidemiology and a practicing trauma center emergency physician. He leads the Behavioral Science and Analytics for Injury Reduction Lab, which applies data science and behavioral economics for preventing injuries from addictive behaviors and substances and for improving acute care. He is developing and testing health system interventions that leverage insights from behavioral economics to promote opioid stewardship for acute and postoperative pain management. He currently leads the acute pain work group of the University Pennsylvania Health System Opioid Task Force. His research is funded by the National Institutes of Health, the U.S. Food and Drug Administration, the U.S. Department of Transportation, and the Agency for Healthcare Research and Quality. He is a Leonard Davis Institute Health Economics Senior Fellow and a faculty member in the Center for Emergency Care Policy and Research, the Center for Health Incentives and Behavioral Economics, the Penn Injury Science Center, and the Children's Hospital of Philadelphia Center for Injury Research and Prevention. He has previously served as a member of the National Academies of Sciences, Engineering, and Medicine's Committee on Accelerating Progress to Reduce Alcohol-Impaired Driving Fatalities. He received his M.D. from the Columbia University College of Physicians and Surgeons and his M.S. in health services research from Stanford University.

Christine D. Greco, M.D., is the clinical director of pain service at Boston Children's Hospital and an assistant professor of anesthesia at Harvard Medical School. Dr. Greco is also the associate program director, Pediatric Pain Medicine Fellowship, at Children's Hospital. Her clinical practice is focused on the management of pain in children, including pelvic pain and endometriosis. Dr. Greco has made presentations on "Opioid Therapy, Pediatric Pain Management and End of Life Care," "Opioids in Adolescents; Principles of Pediatric Anesthesia and Critical Care," and "Managing the Opioid Epidemic in Hospitalized Children." She is a member of the American Society of Anesthesiologists and the American Academy of Pediatrics. Dr. Greco is certified by the American Board of Anesthesiology in pediatric anesthesiology. She received her medical degree from the University of Pittsburgh Medical School, had a pediatric residency at The Ohio State University, and had an anesthesia residency and pediatric anesthesia fellowship at the University of California, San Francisco.

Hillary V. Kunins, M.D., M.P.H., M.S., is the executive deputy commissioner of mental hygiene at the New York City Department of Health and Mental Hygiene. Dr. Kunins leads work in substance use disorders for the department and was the driving force behind implementation of New York City's guidelines for "judicious prescribing" in emergency departments (EDs) and primary care; these guidelines and their implementation provided an impetus to the Centers for Disease Control and Prevention guidelines. Dr. Kunins is the health department lead of HealingNYC, New York City's $60 million comprehensive opioid strategy. Among the key parts of that strategy are how Dr. Kunins has scaled up naloxone distribution to more than 100,000 kits to laypeople; established Relay, an ED-based post-overdose intervention; and overseen provider education about judicious opioid prescribing using academic detailing. She is a frequent speaker on the role of public health in the opioid epidemic and about strategies for clinicians to prevent opioid overdose. Dr. Kunins previously was the program director of residency in primary care/social internal medicine at Montefiore Medical Center/Albert Einstein College of Medicine. She is a fellow of the American Society of Addiction Medicine and in 2017 received the Gary S. Spero Memorial Award for leadership in mental health and substance use treatment from Cornell University. Dr. Kunins received her M.D. and M.P.H. from Columbia University and an M.S. from the Albert Einstein College of Medicine Clinical Research Training Program.

Marjorie C. Meyer, M.D., is the division director of maternal fetal medicine and an attending physician in obstetrics and gynecology at the University of Vermont Medical Center and an associate professor (tenured) in the Department of Obstetrics and Gynecology at the University of Vermont. Dr. Meyer's research interests focus on maternal and newborn sequelae of opioid use in pregnancy: outcomes, opioid use in women, contraception use in opioid-dependent women, and pain control in labor and delivery. She has a grant from the Vermont Child Health Improvement Program to develop a statewide network of care for the treatment of pregnant women with opioid dependence. Dr. Meyer also is engaged in communication with and the education of obstetricians and gynecologists across the state regarding public health initiatives, changes in care models (Blueprint), and quality metrics (vital statistics, statewide database data). She received her medical degree from the University of Florida College of Medicine.

Richard Payne, M.D., was the chair in bioethics at the Center for Practical Bioethics and a professor emeritus in the Duke Divinity School at Duke University. He published extensively in the areas of chronic pain with cancer, neurology, palliative care, end-of-life care and the use of hospice, and access for minorities to pain management. Dr. Payne was a past president of the American Pain Society. He previously gave expert testimony to the Congressional Black Caucus National Brain Trust and the President's Cancer Panel in the area of health care access disparities in cancer care, palliative medicine, and end-of-life care. Dr. Payne was a member of the National Academies of Sciences, Engineering, and Medicine's Board on Health Sciences Policy and a member of the National Academies' Committee on Physician-Assisted Death: Scanning the Landscape and Potential Approaches and the Committee on Advancing Pain Research, Care, and Education. He received his M.D. from Harvard University.

Rosemary C. Polomano, Ph.D., R.N., FAAN, is the associate dean for practice and a professor of pain practice at the University of Pennsylvania School of Nursing. She holds a secondary appointment as a professor of anesthesiology and critical care at the University of Pennsylvania Perelman School of Medicine and is a senior nurse scientist at the Hospital of the University of Pennsylvania. She is also an adjunct professor at the Uniformed Services University of the Health Sciences, Bethesda, Maryland, in the Graduate School of Nursing. Her research focuses on the impact of pain prevention and treatment strategies on short- and long-term pain outcomes with adult postsurgical patients, military service members and veterans, and cancer patients. Dr. Polomano has led research to develop and test patient-reported outcome measures such as the American Pain Society-Patient Outcomes Questionnaire–Revised and the new Defense and Veterans Pain Rating Scale. She has co-authored numerous evidence-based guidelines and consensus reports to advance pain care. She is currently a member of the American Pain Society, the American Academy of Pain Medicine, the Acute Pain Taxonomy, and the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks Acute Neuropathic Pain expert panels. Dr. Polomano is co-director of the University of Pennsylvania's National Institutes of Health–designated center of excellence in pain education, and she leads several pain-related interprofessional education initiatives across the university's health profession schools. In 2014, in recognition of her career-long work to advance pain science, Dr. Polomano received Penn Nursing's Norma M. Lang Award for Scholarly Practice and Policy. She has published more than 100 peer-reviewed journal articles and more than 30 chapters in nursing and medical textbooks. She received her M.S.N. from the University of Pennsylvania and a Ph.D. from the University of Maryland School of Nursing.

Cardinale B. Smith, M.D., Ph.D., is an associate professor of medicine in the Division of Hematology and Medical Oncology and the Brookdale Department of Geriatrics and Palliative Medicine at the Icahn School of Medicine at Mount Sinai and the director of quality for cancer services at Mount Sinai Health

System. She is a clinician investigator whose research interests include evaluating treatment disparities in cancer care, evaluating the determinants of cancer patients' quality of care, characterizing barriers to optimal cancer and palliative care, and developing approaches to eliminating those barriers among racial and ethnic minorities. Dr. Smith is a 2013 recipient of a mentored research scholar grant from the American Cancer Society to evaluate the determinants of disparities in the use of palliative care among patients with lung cancer. Additionally, she is a co-investigator on a Patient-Centered Outcomes Research Institute grant to teach and enable goals of care conversations among oncologists. Dr. Smith has had numerous publications in peer-reviewed journals and is the recipient of the 2014 American Academy of Hospice and Palliative Medicine "Inspiring Hospice and Palliative Medicine Leader under 40" award. She received her M.D. from the Drexel University College of Medicine and Ph.D. from the Graduate School of Biomedical Sciences at the Icahn School of Medicine at Mount Sinai.

Eric C. Sun, M.D., Ph.D., is an assistant professor in the Department of Anesthesiology, Pain, and Perioperative Medicine and (by courtesy) the Department of Health Research and Policy at Stanford University. His research examines the economics of policies related to chronic pain and preoperative medicine and how physician practice organization affects outcomes and costs. He is an associate editor of *Anesthesia and Analgesia*. Dr. Sun has conducted studies on regulating pharmaceutical safety and the effect of behind-the-counter/over-the-counter switches on drug use, prices, and health. He received his Ph.D. in business economics from The University of Chicago Booth Graduate School of Business and an M.D. from The University of Chicago Pritzker School of Medicine, after which he then completed his residency in anesthesiology at Stanford University.

Jennifer F. Waljee, M.D., is an associate professor of surgery in the Department of Surgery of the University of Michigan Health Systems. She specializes in hand surgery, reconstructive surgery, and burn surgery. Her research interests are the incorporation of patient experiences into measures of surgical quality and treatment effectiveness and the application of patient-reported outcomes assessment tools into clinical practice. Dr. Waljee is currently an investigator on several federal- and state-funded grants, including work to explore opioid prescribing and consumption following acute injury and the prevention of iatrogenic opioid dependence after surgery. She serves as a co-director of the Michigan Opioid Prescribing Engagement Network, a statewide quality improvement project dedicated to improving pain and opioid-related outcomes following surgical care. Dr. Waljee is a member of the American College of Surgeons, the American Society of Plastic Surgeons, the American Society for Surgery of the Hand, and the Plastic Surgery Research Council. She currently serves as the director of the Center for Healthcare Outcomes and Policy at the University of Michigan. She is a member of the Centers for Disease Control and Prevention Opioid Prescribing Estimates Workgroup. Dr. Waljee received her M.D. from the Emory University School of Medicine and an M.P.H. from the University of Michigan School of Public Health.

Steven J. Weisman, M.D., currently holds the Jane B. Pettit Chair in Pain Management at the Children's Wisconsin, where he is the medical director of the Jane B. Pettit Pain and Headache Center. In addition, he is a professor of anesthesiology and pediatrics at the Medical College of Wisconsin. Dr. Weisman formerly established and directed pain management programs for children at both the University of Connecticut Health Center and the Yale University School of Medicine. He has completed residency and fellowship training in pediatrics, pediatric hematology–oncology, and anesthesiology. His clinical and research interests focus on the management of postoperative pain in children, exploration of the factors mediating chronic pain in children, and the interface of obesity and chronic pain in children. Dr. Weisman was a member of the American Pain Society, where he served as the chair of the ethics committee.

Previously, he was a liaison representative from the American Academy of Pediatrics to the U.S. Food and Drug Administration's Risk Evaluation and Mitigation Strategies on Long-Acting Opioids. Dr. Weisman received his M.D. from the Albert Einstein College of Medicine.

Charles G. Widmer, D.D.S., is the head of the Division of Facial Pain, Department of Orthodontics, at the University of Florida College of Dentistry. Dr. Widmer's clinical practice includes differential diagnosis of various facial pain conditions with a limited management focus primarily on masticatory musculoskeletal disorders. His research interests include masticatory muscle motor control mechanisms, the biological basis of masticatory muscle pain, and mechanisms of masticatory muscle injury and repair. Dr. Widmer is currently the principal investigator for a study titled "Assessment of opioid use before and after temporomandibular joint implant surgery." He recently chaired an intracollege committee to examine the use of opioids for dental and oral surgery and to bring prescribing practices in line with newer treatment options. Dr. Widmer has served as the chair of numerous special emphasis panels for the National Institute of Dental and Craniofacial Research. He is a member of the American Dental Association, the American Dental Education Association, the International Association for Dental Research (including the Neuroscience Group), and the American Association for Dental Research (including as board member in 2000). Dr. Widmer received his D.D.S. from the Emory University School of Dentistry.

Appendix B

Literature Search Strategies

Below are the literature search strategies used by the committee to identify literature relevant to guidelines and acute pain.

Search Parameters:
Databases: Medline, Embase, Scopus, and PubMed
Date Range: 2000–present

Search Syntax:

Medline (Ovid)

Search No.	Syntax	Results
1	analgesics, opioid/	40,231
2	opioid*.ti,kw.	32,836
3	or/1–2	60,079
4	acute pain/	1,817
5	"acute pain*".ti,kw.	2,066
6	or/4–5	3,330
7	guidance.ti,kw.	13,541
8	guideline adherence/ or guideline/ or practice guideline/	61,534
9	guideline*.ti,kw.	64,417
10	pain management/	30,938
11	management*.ti,kw.	314,186
12	or/7–11	445,705
13	3 and 6 and 12	267
14	limit 13 to (English language and yr="1999–Current")	240

Embase (Ovid):

Search No.	Syntax	Results
1	opiate/	78,111
2	opioid*.ti,kw.	59,499
3	or/1–2	115,459
4	"acute pain*".ti,kw.	4,104
5	guidance.ti,kw.	24,624
6	practice guideline/	385,188
7	guideline*.ti,kw.	113,646
8	medication therapy management/	9,902
9	management*.ti,kw.	495,930
11	3 and 4 and 10	396
12	11	396
13	limit 12 to (English language and yr="1999–Current")	342

PubMed:

("analgesics, opioid"[Mesh] OR opioid[Title] OR opioid[Other Term] OR opioids[Title] OR opioids[Other Term]) AND ("acute pain"[Mesh] OR "acute pain"[Title] OR "acute pain"[Other Term]) AND ("guideline adherence"[Mesh] OR "guideline" [Publication Type] OR "practice guideline" [Publication Type] OR "practice guidelines as topic"[Mesh] OR "pain management"[Mesh] OR guidance[Title] OR guidance[Other Term] OR guideline[Title] OR guideline[Other Term] OR guidelines[Title] OR guidelines[Other Term] OR management[Title] OR management[Other Term])
Publication Dates: 2000/01/01 to 2019/12/31
Languages: English
Results: 293

(opioid[Title] OR opioids[Title]) AND (pain[Title]) AND (guideline*[Title] OR guidance[Title] OR management[Title])
Publication Dates: 2000/01/01 to 2019/12/31
Results: 655

Scopus:

TITLE(opioid* AND "acute pain" AND (guidance OR guideline* OR management*)) OR KEY(opioid* AND "acute pain" AND (guidance OR guideline* OR management)) AND PUBYEAR AFT 1999
Language: English
Results: 285

TITLE(opioid* AND pain AND (guideline* OR guidance)) AND PUBYEAR AFT 1999
Language: English
Results: 107

Search Parameters
Date: 2010–present

Databases Reviewed
Embase
Medline
PubMed
Scopus

Primary Search Terms

Opioid Terms
analgesics, opioid
opiate
opioids

Prescription Opioids
butorphanol
codeine
fentanyl
hydrocodone
hydromorphone
levorphanol
meperidine
methodone
morphine
oxycodone
oxymorphone
tapentadol
tramadol

Acute Pain Terms
accidents
acute pain
alveolopasty
arthroscopic ACL or PCL repair
arthroscopic partial meniscectomy
blast injuries
bone grafting procedures
breast surgery
burns
cardiac catheterization
cardiac surgery
childbirth
cochlear implant
coronary artery bypass grafting (CABG)
dental care
extractions of impacted teeth including third molar
flap procedures

fracture, bone
general surgery
gingivectomy
gynecologic surgery
gynecologic surgical procedures
hysterectomy, minimally invasive
hysterectomy, open
implant surgery
injury
laparoscopic inguinal hernia repair, unilateral
laparoscopic cholecyctectomy
lumpectomy
lumpectomy with sentinel node biopsy
mastectomy, segmental
microdiscectomy (one level)
obstetric surgery
obstetric surgical procedures
open inguinal hernia repair, unilateral
open umbilical hernia repair
ORIF of the ankle
orthropedic surgery
osseous procedures
otolaryngologic surgery
otorhinolaryngologic surgical procedures
parturition
periodontal bone grafting and regeneration procedures
peri-redicular surgery
prostatectomy robotic retro pubic
routine tooth extraction
soft tissue grafting procedures
soft tissue procedures
surgery
surgical extractions
surgical procedures, operative
thoracic surgery
thyroidectomy, partial or total
tooth resection/root amputation
uncomplicated cesarean section
uncomplicated labor and delivery
urologic surgery
urologic surgical procedures
VATS (video assisted thoracotomy)
wounds, gunshots
wounds and injuries

Clinical Practice Guidelines Terms
clinical practice guidelines
practice guidelines as topic
practice patterns, physicians
quality assurance, health care

Alternatives to Opioids Terms
alternative medicine
anesthesia
anti-inflammatory agents, non-steroidal
aspirin
complementary therapies
cyclooxygenase 2 inhibitors
ibuprofen
naproxen
nerve block
opiate substitution treatment
opioid substitution treatment
piroxicam

Database Search Strategies

Embase

Search No.	Search Terms
1	opioids.mp or opiate/
2	*butorphanol/
3	*codeine/
4	*fentanyl/
5	*hydrocodone/
6	*levorphanol/
7	meperidine.mp. or *pethidine/
8	*morphine/
9	*oxycodone/
10	*tapentadol/
11	*hydromorphone/
12	*tramadol/
13	or/1–12
14	*accident/
15	acute pain.mp.
16	*alveoloplasty/
17	*anterior cruciate ligament reconstruction/ or *arthroscopic surgery/
18	*posterior cruciate ligament reconstruction/
19	*blast injury/

Search No.	Search Terms
20	*bone graft/
21	*breast surgery/
22	*burn/
23	cardiac catheterization.mp. or *heart catheterization/
24	cardiac surgery.mp. or *heart surgery/
25	*childbirth/
26	cochlear implant.mp. or *cochlea prosthesis/
27	*coronary artery bypass graft/
28	*dental surgery/
29	*molar tooth/ or *tooth extraction/
30	*third molar/
31	flap procedures.mp.
32	*fracture/
33	*general surgery/
34	*gingivectomy/
35	*gynecologic surgery/
36	*hysterectomy/ or *minimally invasive surgery/
37	*abdominal hysterectomy/
38	*implantation/ or *tooth implantation/ or *tooth implant/ or *implant/
39	injury/
40	*inguinal hernia/ or *laparoscopic surgery/
41	*lumpectomy/
42	*cholecystectomy/
43	*sentinel lymph node biopsy/
44	*partial mastectomy/
45	*lumbar disk hernia/
46	*obstetric operation/
47	*hernioplasty/ or *herniorrhaphy/
48	*umbilical hernia/
49	*ankle fracture/ or *open reduction/
50	surgery/ or *orthopedic surgery/
51	osseous procedures.mp.
52	*ear nose throat surgery/
53	*periodontal disease/ or *alveolar bone loss/
54	*“tooth root”/ or periradicular surgery.mp.
55	*robot-assisted prostatectomy/
56	*tooth extraction/
57	*gingiva disease/

Search No.	Search Terms
58	surgery/
59	thyroidectomy/
60	*endodontic surgery/ or *tooth periapical disease/
61	*cesarean section/
62	*urologic surgery/
63	*video assisted thoracoscopic surgery/
64	*gunshot injury/
65	*battle injury/
66	*maxillofacial surgery/
67	or/14–66
68	clinical practice guidelines.mp. or *practice guideline/
69	dental outcomes.mp.
70	or/68–69
71	13 and 67 and 70
72	limit 71 to yr="2010–2019"

Medline

Search No.	Search Terms
1	opioids.mp. Or *Analgesics, Opioid
2	*BUTORPHANOL/
3	*CODEINE/
4	*FENTANYL/
5	*HYDROCODONE/
6	*LEVORPHANOL/
7	*MEPERIDINE/
8	*MORPHINE/
9	*OXYCODONE/
10	tapentadol.mp.
11	*HYDROMORPHONE/
12	*TRAMADOL/
13	or/1–12
14	*cholecystectomy, laparoscopic/
15	*hernia, inguinal/
16	*hernia, umbilical/
17	*meniscectomy/ or *knee joint/ or *menisci, tibial/ or *knee injuries/ or *osteoarthritis, knee/ or *tibial meniscus injuries/
18	*anterior cruciate ligament/ or *anterior cruciate ligament reconstruction/ or *anterior cruciate ligament injuries/
19	*posterior cruciate ligament/

Search No.	Search Terms
20	*rotator cuff/ or *tendon injuries/ or *rotator cuff injuries/
21	*tibial fractures/ or *ankle injuries/ or *fracture fixation, internal/ or *ankle fractures/ or *open fracture reduction/ or *fractures, bone/
22	*carcinoma, squamous cell/ or *hysterectomy/
23	*minimally invasive surgical procedures/
24	*cesarean section/
25	*prostatectomy/ or *robotic surgical procedures/
26	*mastectomy, segmental/
27	*sentinel lymph node biopsy/ or *lymph node excision/
28	*thoracic surgery, video-assisted/
29	*THYROIDECTOMY/
30	*cochlear implants/
31	*coronary artery bypass/
32	*intervertebral disc displacement/ or microdiscectomy.mp.
33	*tooth extraction/
34	*molar, third/ or *tooth, impacted/
35	*ALVEOLOPLASTY/
36	*bone transplantation/
37	*GINGIVECTOMY/
38	*guided tissue regeneration, periodontal/
39	*gingivoplasty/
40	*dental implants/ or *dental implantation, endosseous/
41	*apicoectomy/
42	*surgery, oral/
43	maxillofacial surgery.mp.
44	tooth resection.mp.
45	*periodontal diseases/
46	*thoracic surgery/
47	*parturition/
48	*gynecologic surgical procedures/
49	*obstetric surgical procedures/
50	*fractures, bone/
51	*otorhinolaryngologic surgical procedures/
52	*general surgery/
53	*surgical procedures, operative/
54	*urologic surgical procedures/
55	or/14–54
56	*“wounds and injuries”/

Search No.	Search Terms
57	*wounds, penetrating/ or *wounds, gunshot/
58	*blast injuries/ or *brain injuries/
59	*burns/
60	or/56–59
61	*acute pain/
62	clinical practice guidelines.mp. or *practice guideline/
63	*practice guidelines as topic/
64	*quality assurance, health care/
65	*practice patterns, physicians'/
66	or/62–65
67	13 and 55 and 66
68	limit 67 to yr="2010–2019"
69	13 and 61 and 66
70	limit 69 to yr="2010–2019"
71	13 and 60 and 66
72	limit 71 to yr="2010–2019"
73	*complementary therapies/
74	*ANESTHESIA/
75	*anti-inflammatory agents, non-steroidal/
76	*ASPIRIN/
77	*cyclooxygenase 2 inhibitors/
78	*IBUPROFEN/
79	*NAPROXEN/
80	*nerve block/
81	*piroxicam/
82	nerve stimulation.mp.
83	or/73–82
84	61 and 66 and 83
85	limit 84 to yr="2010–2019"
86	55 and 66 and 83
87	limit 86 to yr="2010–2019"
88	60 and 61 and 83
89	limit 88 to yr="2010–2019"
90	60 and 66 and 83
91	limit 90 to yr="2010–2019"

Scopus

Opioids and Acute Pain and Clinical Practice Guideline Search
(TITLE-ABS-KEY(opioids or "analgesics, opioid" or opiate or butorphanol or codeine or fentanyl or hydrocodone or levorphanol or meperidine or methodone or morphine or oxycodone or oxymorphone or tapentadol or tramadol or hydromorphone) and pubyear aft 2009) and (TITLE-ABS-KEY(accidents or "acute pain" or "blast injuries" or "breast surgery" or burns or "cardiac surgery" or childbirth or "dental care" or "3rd molar" or alveolopasty or "anterior cruciate ligament reconstruction" or "arthroscopic surgery" or "bone graft" or "cardiac catheterization" or "heart catheterization" or "cardiac surgery" or "heart surgery" or childbirth or "cochlear implant" or "cochlea prosthesis" or "coronary artery bypass graft" or "dental surgery" or "molar tooth" or "tooth extration" or "third molar" or "flap procedures" or fracture or "general surgery" or hysterectomy or "minimally invasive surgery" or "abdominal hysterectomy" or implantation or "tooth implantation" or "tooth implant" or injury or "inguinal hernia" or "laparoscopic surgery" or lumpectomy or cholecystectomy or "sentinel lymphnode biopsy" or "partial mastectomy" or "lumbar disk hernia" or "obstetric operation" or hernioplasty or herniorrhaphy or "umbilical hernia" or "ankle fracture" or "open reduction" or "osseous procedures" or "ear nose throat surgery" or "periodontal disease" or "alveolar bone loss" or "tooth root" or "periradicular surgery" or "robot assisted prostatectomy" or "tooth extraction" or "gingiva disease" or surgery or thyroidectomy or "endodontic surgery" or "tooth periapical disease" or "cesarean section" or "urologic surgery" or "video assisted thoracoscopic surgery" or "gunshot injury" or "battle injury" or "maxillofacial surgery" or parturition or "thoracic surgery" or "gynecologic surgery" or mastectomy or "orthropedic surgery" or "otolaryngologic surgery" and wounds) and pubyear aft 2009) and (TITLE-ABS-KEY("clinical practice guidelines" or {practice guidelines as topic} or "physicians practice patterns" or "practice patterns, physicians" or "quality assurance, health care") and pubyear aft 2009)

Acute Pain and Alternative Medicine Search and Clinical Practice Guideline Search
(TITLE-ABS-KEY (accidents OR "acute pain" OR "blast injuries" OR "breast surgery" OR burns OR "cardiac surgery" OR childbirth OR "dental care" OR "3rd molar" OR alveolopasty OR "anterior cruciate ligament reconstruction" OR "arthroscopic surgery" OR "bone graft" OR "cardiac catheterization" OR "heart catheterization" OR "cardiac surgery" OR "heart surgery" OR childbirth OR "cochlear implant" OR "cochlea prosthesis" OR "coronary artery bypass graft" OR "dental surgery" OR "molar tooth" OR "tooth extraction" OR "third molar" OR "flap procedures" OR fracture OR "general surgery" OR hysterectomy OR "minimally invasive surgery" OR "abdominal hysterectomy" OR implantation OR "tooth implantation" OR "tooth implant" OR injury OR "inguinal hernia" OR "laparoscopic surgery" OR lumpectomy OR cholecystectomy OR "sentinel lymphnode biopsy" OR "partial mastectomy" OR "lumbar disk hernia" OR "obstetric operation" OR hernioplasty OR herniorrhaphy OR "umbilical hernia" OR "ankle fracture" OR "open reduction" OR "osseous procedures" OR "ear nose throat surgery" OR "periodontal disease" OR "alveolar bone loss" OR "tooth root" OR "periradicular surgery" OR "robot assisted prostatectomy" OR "tooth extraction" OR "gingiva disease" OR surgery OR thyroidectomy OR "endodontic surgery" OR "tooth periapical disease" OR "cesarean section" OR "urologic surgery" OR "video assisted thoracoscopic surgery" OR "gunshot injury" OR "battle injury" OR "maxillofacial surgery" OR parturition OR "thoracic surgery" OR "gynecologic surgery" OR mastectomy OR "orthropedic surgery" OR "otolaryngologic surgery" AND wounds) AND PUBYEAR AFT 2009) AND (TITLE-ABS-KEY ("clinical practice guidelines" OR {practice guidelines as topic} OR "physicians practice

patterns" OR "practice patterns, physicians" OR "quality assurance, health care") AND PUBYEAR AFT 2009) AND (TITLE-ABS-KEY ("alternative medicine" OR "opiate substitution treatment" OR anesthesia OR "nerve block" OR "nerve stimulation" OR "anti-inflammatory agents, non-steroidal" OR aspirin OR "complementary therapies" OR "cyclooxygenase 2 inhibitors" OR ibuprofen OR naproxen OR piroxicam OR "acetylsalicylic acid" coxibs OR "anesthesia, spinal" OR "spinal anesthesia" OR "epidural anesthesia" OR "local anesthetics") AND PUBYEAR AFT 2009

PubMed

Opioid and Acute Pain and Clinical Practice Guideline Search
Search (opioids[Title/Abstract] OR opiate[Title/Abstract] OR analgesics, opioid[Title/Abstract] OR butorphanol[Title/Abstract] OR codeine[Title/Abstract] OR fentanyl[Title/Abstract] OR hydrocodone[Title/Abstract] OR levorphanol[Title/Abstract] OR meperidine[Title/Abstract] OR methodone[Title/Abstract] OR oxycodone[Title/Abstract] OR oxymorphone[Title/Abstract] OR tapentadol[Title/Abstract] OR tramadol[Title/Abstract] OR hydromorphone[Title/Abstract])

AND

Search (accidents[Title/Abstract] OR acute pain[Title/Abstract] OR blast injuries[Title/Abstract] OR breast surgery[Title/Abstract] OR burns[Title/Abstract] OR cardiac surgery[Title/Abstract] OR childbirth[Title/Abstract] OR dental care[Title/Abstract] OR 3rd molar[Title/Abstract] OR alveolopasty[Title/Abstract] OR cardiac catheterization[Title/Abstract] OR heart catheterization[Title/Abstract] OR heart surgery[Title/Abstract] OR cochlear implant[Title/Abstract] OR cochlea prosthesis[Title/Abstract] OR coronary artery bypass surgery[Title/Abstract] OR dental surgery[Title/Abstract] OR molar tooth[Title/Abstract] OR tooth extration[Title/Abstract] OR third molar[Title/Abstract] OR flap procedure[Title/Abstract] OR fracture[Title/Abstract] OR general surgery[Title/Abstract] OR hysterectomy[Title/Abstract] OR minimally invasive surgery[Title/Abstract] OR abdominal hysterectomy[Title/Abstract] OR implantation[Title/Abstract] OR tooth implantation[Title/Abstract] OR tooth implant[Title/Abstract] OR injury[Title/Abstract] OR inguinal hernia[Title/Abstract] OR laparoscopic surgery[Title/Abstract] OR lumpectomy[Title/Abstract] OR cholecystectomy[Title/Abstract] OR sentinel lymph node biopsy[Title/Abstract] OR partial mastectomy[Title/Abstract] OR lumbar disk hernia[Title/Abstract] OR obstetric operation[Title/Abstract] OR hernioplasty[Title/Abstract] OR herniorrhaphy[Title/Abstract] OR umblilical hernia[Title/Abstract] OR ankle fracture[Title/Abstract] OR open reduction[Title/Abstract] OR osseous procedures[Title/Abstract] OR ear nose throat surgery[Title/Abstract] OR periodontal disease[Title/Abstract] OR alveolar bone loss[Title/Abstract] OR tooth root[Title/Abstract] OR periradicular surgery[Title/Abstract] OR robot assisted prostatectomy[Title/Abstract] OR tooth extraction[Title/Abstract] OR gingiva disease[Title/Abstract] OR surgery[Title/Abstract] OR thyroidectomy[Title/Abstract] OR endodontic surgery[Title/Abstract] OR tooth periapical disease[Title/Abstract] OR cesarean section[Title/Abstract] OR urologic surgery[Title/Abstract] OR video assisted thoracoscopic surgery[Title/Abstract] OR gunshot injury[Title/Abstract] OR battle injury[Title/Abstract] OR maxillofacial surgery[Title/Abstract] OR parturition[Title/Abstract] OR thoracic surgery[Title/Abstract] OR gynecologic surgery[Title/Abstract] OR mastectomy[Title/Abstract] OR orthopedic surgery[Title/Abstract] OR otolaryngologic surgery[Title/Abstract] OR wounds[Title/Abstract])

AND

Search (clinical practice guidelines[Title/Abstract] OR practice guidelines as topic[Title/Abstract] OR physicians practice patterns[Title/Abstract] OR practice patterns[Title/Abstract] OR quality assurance, health care[Title/Abstract])

Acute Pain and Alternative Medicine and Clinical Practice Guideline Search
Search (accidents[Title/Abstract] OR acute pain[Title/Abstract] OR blast injuries[Title/Abstract] OR breast surgery[Title/Abstract] OR burns[Title/Abstract] OR cardiac surgery[Title/Abstract] OR childbirth[Title/Abstract] OR dental care[Title/Abstract] OR 3rd molar[Title/Abstract] OR alveolopasty[Title/Abstract] OR cardiac catheterization[Title/Abstract] OR heart catheterization[Title/Abstract] OR heart surgery[Title/Abstract] OR cochlear implant[Title/Abstract] OR cochlea prosthesis[Title/Abstract] OR coronary artery bypass surgery[Title/Abstract] OR dental surgery[Title/Abstract] OR molar tooth[Title/Abstract] OR tooth extration[Title/Abstract] OR third molar[Title/Abstract] OR flap procedure[Title/Abstract] OR fracture[Title/Abstract] OR general surgery[Title/Abstract] OR hysterectomy[Title/Abstract] OR minimally invasive surgery[Title/Abstract] OR abdominal hysterectomy[Title/Abstract] OR implantation[Title/Abstract] OR tooth implantation[Title/Abstract] OR tooth implant[Title/Abstract] OR injury[Title/Abstract] OR inguinal hernia[Title/Abstract] OR laparoscopic surgery[Title/Abstract] OR lumpectomy[Title/Abstract] OR cholecystectomy[Title/Abstract] OR sentinel lymph node biopsy[Title/Abstract] OR partial mastectomy[Title/Abstract] OR lumbar disk hernia[Title/Abstract] OR obstetric operation[Title/Abstract] OR hernioplasty[Title/Abstract] OR herniorrhaphy[Title/Abstract] OR umbilical hernia[Title/Abstract] OR ankle fracture[Title/Abstract] OR open reduction[Title/Abstract] OR osseous procedures[Title/Abstract] OR ear nose throat surgery[Title/Abstract] OR periodontal disease[Title/Abstract] OR alveolar bone loss[Title/Abstract] OR tooth root[Title/Abstract] OR periradicular surgery[Title/Abstract] OR robot assisted prostatectomy[Title/Abstract] OR tooth extraction[Title/Abstract] OR gingiva disease[Title/Abstract] OR surgery[Title/Abstract] OR thyroidectomy[Title/Abstract] OR endodontic surgery[Title/Abstract] OR tooth periapical disease[Title/Abstract] OR cesarean section[Title/Abstract] OR urologic surgery[Title/Abstract] OR video assisted thoracoscopic surgery[Title/Abstract] OR gunshot injury[Title/Abstract] OR battle injury[Title/Abstract] OR maxillofacial surgery[Title/Abstract] OR parturition[Title/Abstract] OR thoracic surgery[Title/Abstract] OR gynecologic surgery[Title/Abstract] OR mastectomy[Title/Abstract] OR orthopedic surgery[Title/Abstract] OR otolaryngologic surgery[Title/Abstract] OR wounds[Title/Abstract])

Search (clinical practice guidelines[Title/Abstract] OR practice guidelines as topic[Title/Abstract] OR physicians practice patterns[Title/Abstract] OR practice patterns[Title/Abstract] OR quality assurance, health care[Title/Abstract])

Search (alternative medicine[Title/Abstract] OR opiate substitution treatment[Title/Abstract] OR anesthesia[Title/Abstract] OR nerve block[Title/Abstract] OR nerve stimulation[Title/Abstract] OR anti-inflammatory agents, non-steroidal[Title/Abstract] OR aspirin[Title/Abstract] OR complementary therapies[Title/Abstract] OR cyclooxygenase 2 inhibitors[Title/Abstract] OR ibuprofen[Title/Abstract] OR naproxen[Title/Abstract] OR piroxicam[Title/Abstract] OR acetylsalicyclic acid coxibs[Title/Abstract] OR anesthesia, spinal[Title/Abstract] OR spinal anesthesia[Title/Abstract] OR epidural anesthesia[Title/Abstract] OR local anesthetics[Title/Abstract])

Appendix C

Public Session Agendas

February 4, 2019

8:30 AM **Registration**

9:00–9:15 AM **Welcome and Opening Remarks**
Bernard Lo, The Greenwall Foundation
Committee Chair

9:15–9:45 AM **FDA's Goals for the National Academies Study**
Douglas Throckmorton, U.S. Food and Drug Administration, Center for Drug Evaluation and Research

9:45–10:45 AM **Session 1: Medical Indications for Which Opioids Prescribing Guidelines for Acute Management Should Be Available**
Moderator: Hillary Kunins, New York City Department of Health and Mental Hygiene

Panelists:

- Joanna Starrels, Albert Einstein College of Medicine
- Steven Brown, University of Arizona College of Medicine (via Zoom)
- Ula Hwang, Icahn School of Medicine at Mount Sinai
- Leslie Bisson, University at Buffalo

Questions from Committee to Panelists

10:45–11:00 AM **Break**

11:00 AM–12:00 PM **Session 2: Surgical Indications for Which Opioid Prescribing Guidelines for Acute Management Should Be Available (Includes Dental and Pediatric Indications)**
Moderator: Jennifer Waljee, University of Michigan School of Medicine

Panelists:

- Richard Barth, Jr., Dartmouth-Hitchcock Medical Center
- Kevin Bozic, The University of Texas at Austin Dell Medical School
- Clifford Ko, University of California, Los Angeles, School of Medicine
- Elliot Krane, Stanford University
- Lisa Leffert, Massachusetts General Hospital
- Paul Moore, University of Pittsburgh School of Dental Medicine

Questions from Committee to Panelists

12:00–12:15 PM **Public Comments from In-Person and Remote Workshop Participants**

12:15–1:30 PM **Lunch**

1:30–2:35 PM **Session 3: Overlapping Indications and Issues for Opioid Prescribing for Acute Pain**
Moderator: Steven Weisman, Children's Wisconsin

Panelists:

- Richard Barth, Jr., Dartmouth-Hitchcock Medical Center
- Leslie Bisson, University at Buffalo
- Kevin Bozic, The University of Texas at Austin Dell Medical School
- Steven Brown, University of Arizona College of Medicine (via Zoom)
- Ula Hwang, Ichan School of Medicine at Mount Sinai
- Clifford Ko, University of California, Los Angeles, School of Medicine
- Elliot Krane, Stanford University
- Lisa Leffert, Massachusetts General Hospital
- Paul Moore, University of Pittsburgh School of Dental Medicine
- Joanna Starrels, Albert Einstein College of Medicine

Questions from Committee to Panelists

2:35–2:45 PM **Public Comments from In-Person and Remote Workshop Participants**

2:45–3:00 PM **Break**

3:00–4:35 PM **Session 4: Challenges and Opportunities to Developing Evidence-Based Clinical Practice Guidelines for Acute Pain**
Moderator: Roger Chou, Oregon Health & Science University School of Medicine

Panelists:

- Richard Barth, Jr., Dartmouth-Hitchcock Medical Center
- Holger Schünemann, Grading of Recommendations Assessment, Development and Evaluation and McMaster University
- Paul Shekelle, University of California, Los Angeles, School of Medicine (via Zoom)
- Debra Houry, Centers for Disease Control and Prevention
- Doug Owens, U.S. Preventive Services Task Force and Stanford University (via Zoom)

Questions from Committee to Panelists

4:35–4:45 PM **Public Comments from In-Person and Remote Workshop Participants**

4:45 PM **Closing Comments**
Bernard Lo, The Greenwall Foundation
Committee Chair

5:00 PM **Adjourn**

July 9, 2019

8:30 AM **Registration**

9:00–9:15 AM **Welcome and Opening Remarks**
Bernard Lo, The Greenwall Foundation
Committee Chair

9:15–10:45 AM **Session 1: Identifying Research Gaps in Opioids Prescribing Guidelines for Acute Pain Management in Medical Indications**
Moderator: Mark Bicket, Johns Hopkins University

Speakers

- Sickle Cell Disease/Crisis: Wally Smith, Virginia Commonwealth University
- Musculoskeletal Pain: Benjamin Friedman, Albert Einstein College of Medicine
- Kidney Stones: David Goldfarb, New York University School of Medicine

Discussion with and Q&A from the Committee

10:45–11:00 AM **Break**

11:00 AM–12:30 PM **Session 2: Identifying Research Gaps in Opioids Prescribing Guidelines for Acute Pain Management Following Surgical Procedures**
Moderator: Marjorie Meyer, University of Vermont Medical Center

Speakers

- Cesarean Section and Vaginal Delivery: Brian Bateman, Brigham and Women's Hospital
- Knee Replacement Surgery: David Jevsevar, Dartmouth Geisel School of Medicine
- Wisdom Teeth Extraction: Elliot Hersh, University of Pennsylvania School of Dental Medicine

Discussion with and Q&A from the Committee

12:30–1:15 PM **Lunch**

1:15–2:30 PM **Session 3: Gaps in Evidence for Clinical Practice Guidelines**
Moderator: Eric Sun, Stanford University

Speakers

- Elizabeth Habermann, Mayo Clinic
- Darshak Sanghavi, OptumLabs

Discussion with and Q&A from the Committee

2:30–2:45 PM **Public Comments from In-Person and Remote Workshop Participants**

2:45 PM **Closing Comments**
Bernard Lo, The Greenwall Foundation
Committee Chair

3:00 PM **Adjourn**